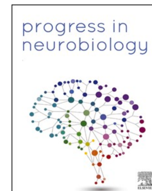
Progress in Neurobiology 204 (2021) 102112

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio



Review article

Autophagy as a gateway for the effects of methamphetamine: From neurotransmitter release and synaptic plasticity to psychiatric and neurodegenerative disorders

Fiona Limanaqi [a], Carla L. Busceti [b], Roberta Celli [b], Francesca Biagioni [b], Francesco Fornai [a,b,*]

[a] Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Via Roma, 55, 56126, Pisa, PI, Italy
[b] IRCCS Neuromed, Via Atinense 18, 86077 Pozzilli, IS, Italy

ARTICLE INFO

Keywords:
Dopamine
Addiction
Psychosis
Parkinsonism
LC3
mTOR
GSK3-β
PKC
CDK5

ABSTRACT

As a major eukaryotic cell clearing machinery, autophagy grants cell proteostasis, which is key for neurotransmitter release, synaptic plasticity, and neuronal survival. In line with this, besides neuropathological events, autophagy dysfunctions are bound to synaptic alterations that occur in mental disorders, and early on, in neurodegenerative diseases. This is also the case of methamphetamine (METH) abuse, which leads to psychiatric disturbances and neurotoxicity. While consistently altering the autophagy machinery, METH produces behavioral and neurotoxic effects through molecular and biochemical events that can be recapitulated by autophagy blockade. These consist of altered physiological dopamine (DA) release, abnormal stimulation of DA and glutamate receptors, as well as oxidative, excitotoxic, and neuroinflammatory events. Recent molecular insights suggest that METH early impairs the autophagy machinery, though its functional significance remains to be investigated. Here we discuss evidence suggesting that alterations of DA transmission and autophagy are intermingled within a chain of events underlying behavioral alterations and neurodegenerative phenomena produced by METH. Understanding how METH alters the autophagy machinery is expected to provide novel insights into the neurobiology of METH addiction sharing some features with psychiatric disorders and parkinsonism.

Abbreviations: AADC, aromatic amino acid decarboxylase; AD, aldehyde dehydrogenase; AGE, advanced glycation end-product; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; AMPK, 5′ AMP-activated protein kinase; Atg, autophagy-related gene; BBB, blood-brain barrier; BECN1, beclin 1; cAMP, cyclic adenosine monophosphate; CDK5, cyclin-dependent kinase 5; CMA, chaperone-mediated autophagy; CNS, central nervous system; CREB, cAMP response element binding protein; CRMP2, collapsin response mediator protein-2; DA, dopamine; DAMPs, damage-associated molecular patterns; DAT, dopamine transporter; DISC1, disrupted in schizophrenia 1; DOPAC, 3,4-dihydroxyphenylacetic acid; DOPALD, 3,4-dihydroxyphenylacetaldehyde; DPYSL2, dihydropyrimidinase-like 2; DRD1, type 1-dopamine receptor; DRD2, type 2-dopamine receptor; DβH, dopamine β hydroxylase; FOXO3, transcription factor forkhead box O3; GABA, gamma-aminobutyric acid; GFAP, glial fibrillary acidic protein; GLUT, glutamate; GSK3-β, glycogen synthase kinase beta; HD, Huntington's disease; HMGB1, high-mobility group box-1; Hsc70, heat shock cognate 71 kDa protein; ICAM-1, cellular adhesion molecule; IL-1β, interleukin 1β; IL-6, interleukin 6; MAO, monoamine-oxidase; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemo-attractant protein 1; METH, methamphetamine; MIC, microautophagy; MMP-9, matrix metalloproteinase-9; MUD, methamphetamine use disorder; MSNs, medium-sized spiny neurons; mTOR, mammalian/mechanistic target of rapamycin; NE, norepinephrine; NF-κB, nuclear factor-kappa B; NLRP3, Nod-like Receptor Protein 3; NMDAR, N-Methyl-D-aspartate receptor; NOX2, NAD(P)H oxidase 2; NRF-2, nuclear factor erythroid 2 (NFE2)-related factor 2; PD, Parkinson's disease; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3P, phosphatidylinositol 3-phosphate; PKC, protein kinase c; RAGE, receptor for advanced glycation end-product; RVLM, rostral ventrolateral medulla; SNpc, substantia nigra *pars compacta*; TFAM, mitochondrial transcription factor A; TFEB, transcription factor EB; TH, tyrosine hydroxylase; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; UPS, ubiquitin-proteasome system; VCAM-1, vascular cell adhesion molecule 1; VMAT-1/2, vesicular monoamine transporter type-1/2; VPS34, vacuolar protein sorting 34; VPS35, vacuolar protein sorting 35; VTA, ventral tegmental area; 5-HT, 5-hydroxytryptamine, serotonin.

* Corresponding author at: Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Via Roma, 55, 56126, Pisa, PI, Italy.

E-mail address: francesco.fornai@unipi.it (F. Fornai).

https://doi.org/10.1016/j.pneurobio.2021.102112
Received 7 December 2020; Received in revised form 27 February 2021; Accepted 18 June 2021
Available online 23 June 2021
0301-0082/© 2021 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

Interconnections have been documented between the effects of the widely addictive and neurotoxic drug methamphetamine (METH), and the autophagy machinery, which grants synaptic plasticity besides neuronal survival (Birdsall and Waites, 2019). While consistently altering the autophagy machinery (Larsen et al., 2002; Lin et al., 2012; Lazzeri et al., 2018), METH produces multifaceted, and long-lasting effects in the human/animal brain. These include psychomotor alterations, such as hyper-locomotion, and stereotypies, addiction, depression, eating disorders, psychosis, memory impairment, and altered cortical excitability (Meredith et al., 2005; Homer et al., 2008; Brown et al., 2011; Glasner-Edwards et al., 2011; Cadet and Bisagno, 2016). All these effects vary over time following reiterated drug exposure, and they may occur as the consequence of neurotoxicity or epigenetic and transcriptional changes fostering drug-induced behavioral sensitization (Nestler, 2001; Godino et al., 2015; Moratalla et al., 2017; Robinson and Berridge, 2008) This involves mostly the dopamine (DA) mesostriatal and mesocorticolimbic brain systems. Repeated/high doses of METH deplete striatal DA, which is due to a loss of nigrostriatal DA terminals, and as occasionally documented, of cell bodies within the substantia nigra *pars compacta* (SNpc) (Ares-Santos et al., 2014; Biagioni et al., 2019; Kitamura, 2009; Liu and Dluzen, 2006; Hirata and Cadet, 1997). METH toxicity against DA axons and cell bodies largely relates to an increase in oxidative species that impair proteostasis and mitochondrial function while promoting neuroinflammation and apoptosis (Cadet et al., 1994; Jayanthi et al., 1998, 2001, 2004, 2005; Thomas et al., 2008; Limanaqi et al., 2018b). Within DA cells and nigral cell bodies, METH produces cytoplasmic alterations which also extend to the cytoplasm and nucleus of striatal GABA neurons (Fornai et al., 2003, 2004; Lazzeri et al., 2006, 2007; Lin et al., 2012; Li et al., 2017; Ferrucci et al., 2017). These consist of protein inclusions staining for heat shock proteins, as well as autophagy and proteasome substrates, such as ubiquitin, parkin, alpha-synuclein, tau, and prion protein. Such alterations are partly reminiscent of those detected within DA and hippocampal neurons of METH abusers (Quan et al., 2004; Kitamura, 2009). However, direct evidence relating these alterations to autophagy or proteasome specifically in the post-mortem brain of METH users is lacking so far.

It is fascinating that beyond both frank proteinopathy and neurotoxicity, which may occur during METH administration/intake, autophagy alterations are also bound to innumerous neurochemical, oxidative, and neuroinflammatory events. These are known to sustain METH-induced behavioral sensitization, aside from them being implicated in some mental disorders and neurodegenerative diseases (Da Luz et al., 2015; Du et al., 2017; Krasnova et al., 2016; McCutcheon et al., 2019; Puri and Subramanyam, 2019; Ryskalin et al., 2018). This is not surprising since autophagy intermingles with the proteasome system and secretory/trafficking pathways to control behavior. This occurs through the turnover of synaptic components and modulation of neurotransmitters that are implicated in METH-induced addiction, including DA, glutamate (GLUT), and GABA (Hernandez et al., 2012; Shehata et al., 2012; Limanaqi et al., 2018a; Hui and Tanaka, 2019). In turn, dysfunctions of various synaptic proteins and the occurrence of non-canonical biochemical pathways that are bound to the effects of METH, converge in altering both neurotransmission and autophagy (Beaulieu et al., 2009; Hong and Amara, 2013; Limanaqi et al., 2018a; Murdoch et al., 2016; Wang et al., 2015, 2018). Rescuing autophagy is pivotal for the survival of catecholamine and in particular, DA neurons that are highly susceptible to DA-related oxidative damage, as that induced by METH (Castino et al., 2008; Da Luz et al., 2015; Wei et al., 2016; Sun et al., 2019). In line with this, compounds that are known to act as autophagy inducers, have been shown to counteract both METH-induced behavioral sensitization and neurotoxicity (Ago et al., 2012; Beaulieu et al., 2004; Huang et al., 2018; Lazzeri et al., 2018; Li et al., 2017). Some of these compounds are increasingly shown to possess antidepressant, mood-stabilizing, or antipsychotic effects which are partly bound to autophagy activation (Zhang et al., 2007; Gassen and Rein, 2019; Ryskalin et al., 2018). This is in line with evidence that loss of autophagy can disrupt neuronal cell biology and predispose to behavioral changes including psychotic-like symptoms, and cognitive alterations, up to neurodegeneration (Hara et al., 2006; Hu et al., 2017; Merenlender-Wagner et al., 2015; Sato et al., 2018; Schneider et al., 2016).

This suggests that rescuing autophagy in the brain may produce plastic effects that relate to both behavioral improvements and neuroprotection against METH neurotoxicity. Notwithstanding these pieces of evidence, controversial results and confounding outcomes still exist on the autophagy status during METH administration. Therefore, the role of the autophagy cascade in regulating neurotransmission and cell survival within METH-affected brain structures will be here analyzed in an attempt to correlate autophagy alterations with the maladaptive plastic changes sustaining addiction. This extends to degenerative phenomena that occur during METH abuse. Such an analysis will encompass (i) an overview of the anatomical and molecular targets of METH, and hints to the role of autophagy; (ii) molecular and biochemical pathways linking autophagy and synaptic plasticity; (iii) evidence on autophagy-based modulation of DA-related behavior, which is critical for METH-induced addiction; (iv) past controversies and novel insights on the fine molecular mechanisms through which METH alters the autophagy machinery; v) bridging METH-induced autophagy alterations and neurotoxic degenerative phenomena; vi) role of autophagy in METH-induced neuroinflammation. The present knowledge discussed here is expected to provide novel experimental clues on the role of cell-clearing systems in METH-induced addiction and neurotoxicity, with potential implications for some DA-related psychiatric and neurodegenerative diseases.

2. METH-induced behavioral sensitization: hints to the role of autophagy

METH is a widely abused psychostimulant owning powerful addictive and neurotoxic potential. The drug rapidly enters the central nervous system (CNS) where it persists for up to 12 h (Fowler et al., 2008; Volkow et al., 2010a). The drug kinetics in the CNS (and mostly within monoamine-containing brainstem nuclei projecting to the limbic system) parallel the acute effects of METH in both animals and humans. These consist of euphoria, excitation, subjective perception of increased energy, motor stimulation, active waking state, sleeplessness, and alertness (Stephans and Yamamoto, 1995; Cruickshank and Dyer, 2009; Marshall and O'Dell, 2012; Radfar and Rawson, 2014). Reiterated intake/administration of METH produces long-lasting alterations, which may be the consequence of neurotoxicity or persistent, epigenetic and transcriptional changes driving maladaptive plasticity within striatal, limbic, and isocortical brain areas (Uehara et al., 2004; Battaglia et al., 2002a, b; Godino et al., 2015; Limanaqi et al., 2018b; Moratalla et al., 2017; Li et al., 2015). Reiterated intake/administration of METH induces a compulsive pattern of drug-taking behaviors, which produces long-lasting neuronal adaptations making reward and motivation brain systems hypersensitive to drug and drug-associated stimuli (Nestler, 2001; Robinson and Berridge, 2000, 2008). This is bound to the onset of drug-induced behavioral sensitization, which translates into long-lasting psychomotor effects such as stereotypies, addiction, craving, aggressiveness, bulimia and anorexia, psychosis, depression, cognitive impairments, and altered cortical excitability (Zweben et al., 2004; Meredith et al., 2005; Homer et al., 2008; Hoffman et al., 2006; McKetin et al., 2006; Brown et al., 2011; Glasner-Edwards et al., 2011; Marshall and O'Dell, 2012; Hadamitzky et al., 2012; Dean et al., 2013; Radfar and Rawson, 2014; Glasner-Edwards and Mooney, 2014; Cadet and Bisagno, 2016; Ferrucci et al., 2019). At the molecular level, activation of the cAMP/AKT pathway, as well as CREB and ΔFosB provides a mechanism of addiction based on the stability of these proteins, by which drug-induced changes in gene expression within striatal neurons can

persist long after drug withdrawal (Nestler, 2001; Robison and Nestler, 2011; Li et al., 2015). Again, reduced protein degradation, regulation of receptor sensitivity, along with structural changes, such as increased spine density within the neurons of the mesolimbic DA system and their targets, are key modifications that occur after repeated drug administration (Nestler, 2001; Robison and Nestler, 2011; Li et al., 2015).

The biochemical basis underlying this phenomenon is largely due to altered synaptic transmission at the level of monoamine, mainly the DA brain system (Lazzeri et al., 2007; Sulzer, 2011). In fact, as measured by brain dialysis, reiterated METH administration in mice produces dramatic oscillations of extracellular DA, which ranges from high peaks (exceeding by 10-fold baseline levels) to severe deficiency (no detectable extracellular levels) within just a few hours (Battaglia et al., 2002a, b; Lazzeri et al., 2007). This surpasses at large the slight oscillations produced by physiological DA release to produce abnormal, pulsatile stimulation of postsynaptic DA receptors (DRs). This involves mostly type 1 DRs (D1DRs), which in turn, trigger non-canonical transduction pathways that alter the responsivity of postsynaptic neurons to sustain drug addiction (Merchant et al., 1988; Centonze et al., 2003; Fleckenstein et al., 2007; Li et al., 2015; Limanaqi et al., 2018b, 2019; Cadet et al., 2012; Surmeier et al., 2010). This occurs within reward-related brain areas where DA terminals are most abundant, namely the medium-sized spiny neurons (MSNs) of the striatum, although limbic and isocortical brain regions are involved as well (Fig. 1, Volkow and Morales, 2015).

The alterations in physiological DA release, in time, amount, and place, represent a major determinant of both the behavioral syndrome occurring immediately after METH intake and the long-term behavioral changes that reflect mainly the persistent alterations in postsynaptic DA brain regions following chronic METH exposure. METH use disorder (MUD) is characterized by the occurrence and relapse of neuropsychological symptoms which may widely contribute to exacerbating preexisting neuropsychological deficits and comorbid neurological or psychiatric disorders (Volkow, 2009; Glasner-Edwards and Mooney, 2014; Cadet and Bisagno, 2016). The neurobehavioral effects of METH-induced sensitization are recapitulated at the neurochemical level, since abnormal DA synthesis, release, and re-uptake, along with the abnormal activity of DRs are bound to psychiatric symptoms occurring in MUD, as postulated for some mental disorders as well (Abi-dargham and Moore, 2003; Howes et al., 2012; Laruelle et al., 1999; Perreault et al., 2010; Ryskalin et al., 2018; Weidenauer et al., 2017).

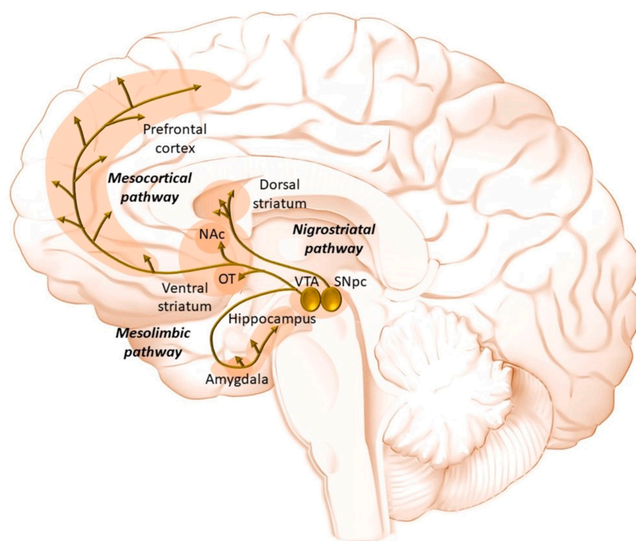


Fig. 1. DA pathways and target brain areas affected by METH. Both the short-term and long-term behavioral effects of METH stem from altered DA transmission within the mesostriatal, nigrostriatal, mesolimbic, and mesocortical pathways projecting to the ventral and dorsal striatum, limbic brain areas (amygdala and hippocampus), and the prefrontal cortex, respectively. The ventral striatum, which comprises the NAc (Nucleus Accumbens); and OT (olfactory tubercle), is mostly involved in goal-directed behavior, while the dorsal striatum in the habit-based behavior induced by METH. METH neurotoxicity mostly affects striatal DA terminals arising from the SNpc (substantia nigra pars compacta) though it may also extend to neuronal cell bodies within the SNpc, and as occasionally documented, within the VTA (ventral tegmental area), striatum, and hippocampus.

In this frame, it is remarkable that impairment of autophagy machinery within DA neurons of experimental animals leads to increased evoked striatal DA secretion along with decreased DA re-uptake, in a way reminiscent of the mechanisms of action of METH (Hernandez et al., 2012; Hunn et al., 2019). Again, autophagy is variously affected by abnormal stimulation of DRs, with D1DR inhibiting the autophagy flux while largely contributing to METH addiction (Wang et al., 2018; Yang et al., 2020a, b). Furthermore, several synaptic proteins, and susceptibility genes for mental disorders, do converge on autophagy-related pathways (Limanaqi et al., 2018a; Ryskalin et al., 2018; Section 3.2). Intriguingly, these are mostly involved in pre-synaptic DA release and those post-synaptic DR-related cascades that are altered by METH. In line with this, mTOR or GSK3-β inhibitors, and/or AMPK/TFEB inducers, which are known to promote autophagy, revert DA-related behavioral sensitization, memory impairment, and morphological alterations that are produced by METH (Ago et al., 2012; Beaulieu et al., 2004; Castino et al., 2008; Xu et al., 2011; Huang et al., 2018; Lazzeri et al., 2018; Li et al., 2017; Yan et al., 2019). Again, these compounds are shown to produce antipsychotic, antidepressant, or antimanic effects (Cleary et al., 2008; Kara et al., 2013, 2018; Kim et al., 2018; Mai et al., 2018; Ryskalin et al., 2018; Zhang et al., 2007). Such an issue is discussed in depth ahead when focusing on METH-related molecular and biochemical events with which autophagy is intermingled (Section 3). Here, we wish to anticipate that METH may produce detrimental effects bridging alterations in DA neurotransmission and cell clearing systems. This may extend well beyond neuroprotection against METH toxicity to sustain METH-related behavioral sensitization. Most of the research aimed at dissecting the effects of METH upon the autophagy machinery is based on toxicity studies, correlating autophagy with the cytopathological and apoptotic effects of METH. Despite increasing evidence linking autophagy dysfunctions, neurotransmitter release, synaptic plasticity, and neuropsychiatric alterations, studies investigating the role of autophagy in the behavioral effects of METH specifically are missing so far. Here we bring together direct and indirect evidence joining the plastic and neuroprotective effects of the autophagy machinery in brain structures that are targeted by METH, with a primary focus on the DA system. Before moving to such an issue, the molecular targets of METH within DA neurons are briefly summarized to ease comprehension of the intermingling effects of autophagy with DA metabolism and secretory machinery.

2.1. *Molecular effects of METH in monoamine-containing neurons, a focus on dopamine*

The bases for the effects of METH stem from a quite selective uptake and the presence of common intracellular targets within monoamine-containing neurons, which in turn, produce widespread innervation within a variety of brain areas where the effects of METH are ultimately produced.

Within monoamine neurons, the effects of METH stem from its interaction with three molecular targets, namely 1) the synaptic vesicles and the vesicular monoamine transporter type-2 (VMAT-2), 2) the monoamine transporters, namely DA transporter (DAT), norepinephrine (NE) transporter (NET), and serotonin (or 5-hydroxytryptamine, 5-HT) transporter (SERT), and 3) mitochondrial electron transport chain complexes, and monoamine oxidase (MAO) enzyme, which carries out monoamine oxidative deamination. The activities of all these proteins

are impaired by METH once it enters DA/NE/5-HT terminals via either monoamine transporters or passive diffusion. Although most of this evidence emerges from studies carried out within DA-containing neurons, it is worth mentioning that METH-induced addiction, psychotic signs, and memory deficits are also bound to alterations of NE, and 5-HT and their transporters (Weinshenker and Schroeder, 2007; Reichel et al., 2012; McFadden et al., 2012, 2018; Ferrucci et al., 2019).

VMAT-2 selectively recognizes and transports cytosolic monoamines DA, NE, and 5-HT within synaptic vesicles (Erickson et al., 1996). Contrarily to VMAT-1 being expressed within both neuronal and non-neuronal cells (e.g. chromaffin cells of the adrenal medulla), VMAT-2 is most abundantly expressed in the brain, with a higher affinity for DA and NE compared with VMAT-1 (Erickson et al., 1996). VMAT-2 plays a key role in cytosolic catecholamine homeostasis and release since it guarantees the vesicular packaging and storage of both newly synthesized and synapse-recycled DA. This grants the compartmentalized physiological oxidative deamination of DA, which is key to preventing DA self-oxidation and production of reactive DA by-products, such as DA-quinones. Within DA-storing synaptic vesicles, METH acts as a weak base to disrupt the proton gradient and rise the acidic compartment towards basic values, which makes nonpolar DA freely diffusible out of the vesicles (Cubells et al., 1994; Sulzer and Rayport, 1990; Sulzer, 2011). Again, METH directly inhibits VMAT-2 and displaces VMAT-2 molecular complex from synaptic vesicle membranes to non-canonical membranous compartments, such as those of the trans-Golgi network (Brown et al., 2000; Sandoval et al., 2002, 2003). These events prevent DA from re-entering the vesicles meanwhile impairing physiological DA storage, which generates massive levels of extra-vesicular DA within axons (Fleckenstein et al., 2007; Guillot et al., 2008; Volz et al., 2007). METH-induced alkalization per se may not be sufficient to fully produce the typical redistribution of vesicular DA, thus its action as a weak base to tone down the vesicular pH gradient must be coupled with the selective inhibition of VMAT-2. In fact, bafilomycin, which acts as a proton pump inhibitor only with no effects on VMAT-2, redistributes only half of METH-induced DA levels in the extracellular compartment, despite decreasing the pH ratio vesicle/cytoplasm by 2-fold compared with METH alone (Floor and Meng, 1996). While increasing cytosolic DA levels through a collapse in secretory vesicle pH gradients, prolonged exposure to amphetamines and other weak bases produces a compensatory response resulting in vesicle acidification, which enhances vesicular catecholamine release and quantal size during fusion events (Markov et al., 2008). Similar to what documented in both experimental models and human METH abusers, VMAT-2 is reduced in the brains of animal models and subjects with Parkinson's disease (PD) or psychiatric disorders (Miller et al., 1999; Mooslehner et al., 2001; Kitamura, 2009; Iritani et al., 2010; McFadden et al., 2012; Purves-Tyson et al., 2017).

Within the cytosol, METH also acts at the level of mitochondria where it inhibits mitochondrial respiratory chain complexes (Brown et al., 2005; Ruan et al., 2020), and the MAO enzyme on the outer mitochondrial membrane (Gesi et al., 2001; Liu et al., 2016; Suzuki et al., 1980). MAO carries out the oxidative deamination of DA, NE, and 5-HT, and exists as two different isoforms, namely MAO-A and MAO-B. The former is present within catecholamine-containing neurons (DA, NE, and Epinephrine neurons), whereas the latter occurs mainly in 5-HT-containing and glial cells. Remarkably, METH inhibits MAO-A with a 10-fold higher affinity compared with MAO-B, which underlines the crucial role of MAO-A for METH-induced alterations of intracellular DA metabolism within DA terminals (Gesi et al., 2001; Suzuki et al., 1980). This may also include the uncoupling between MAO-A and aldehyde dehydrogenase (AD), thus occluding the AD-dependent conversion of the highly reactive by-product of DA oxidation 3,4-dihydroxyphenylacetaldehyde (DOPALD) into the quite inert 3,4-dihydroxyphenylacetic acid (DOPAC) (Agid et al., 1973; Gesi et al., 2001). Joined with the actions of VMAT-2 and DAT mediating DA uptake within the nerve terminals and within synaptic vesicles, respectively, this represents the most powerful system to surveil DA activity. In the absence of a compartmentalized physiological oxidative deamination, which occurs following METH administration, DA self-oxidation produces a high amount of reactive aldehyde DOPALD, which owns a dramatic oxidative potential and quickly interacts with various cell substrates within the DA axon terminals and surrounding compartments (Gesi et al., 2001). Again, self-oxidative DA metabolism leads to the generation of toxic quinones and highly reactive chemical species such as hydrogen peroxide (H_2O_2) and superoxide radicals, which react with sulfhydryl groups and promote structural modifications by targeting oxidation-prone domains within proteins, lipids, and nucleic acids (Cadet et al., 1994; Cubells et al., 1994; Gluck et al., 2001; Guillot et al., 2008; Jayanthi et al., 1998; LaVoie and Hastings, 1999; Sulzer and Zecca, 1999; Lazzeri et al., 2007; Miyazaki et al., 2006). Such powerful oxidative stress within presynaptic DA terminals is key to fostering nigrostriatal toxicity. At the same time, cytosolic presynaptic DA diffuses in the extracellular space either by passive diffusion or via the reverted direction of DAT, an additional effect which is promoted by METH (Fig. 2, Schmidt and Gibb, 1985; Sulzer, 2011; Sulzer and Rayport, 1990; Volz et al., 2007).

In fact, METH impairs the plasma membrane DAT which selectively takes up extracellular DA within nerve terminals (McFadden et al., 2012; Volz et al., 2007). METH impairs DAT activity either via direct inhibition or via reverting its direction, which potentiates the accumulation of freely diffusible DA in the extracellular space (Schmidt and Gibb, 1985; Sulzer, 2011; Sulzer and Rayport, 1990; Volz et al., 2007). Similar to what occurs in the animal and human METH-addicted brain, reduced DAT expression was detected in animal models and subjects with psychiatric disorders or PD (Wilson et al., 1996; Miller et al., 1999; Kitamura, 2009; McCann et al., 2008; McFadden et al., 2012; Markota et al., 2014; Purves-Tyson et al., 2017; Volkow and Morales, 2015; Chang et al., 2020). METH-induced impairment and downregulation of DAT lead to unusually high extracellular DA levels, which produces synaptic effects at both short and long-distance through a volume transmission (Fuxe et al., 2010). This encompasses striatal MSNs, and non-neuronal targets such as the neurovascular unit, which is implicated in the neuroinflammatory effects of METH administration (Northrop and Yamamoto, 2015). In fact, METH-induced damage to DA terminals is accompanied or even preceded by extensive neuroinflammation and gliosis, which may contribute to blood-brain barrier damage and neurodegeneration over prolonged periods.

Catecholamine, and mostly DA neurons, which are massively, and quite selectively recruited by stressful events and abused substances, do share common morphology and metabolic features, which may explain their susceptibility to neurodegenerative phenomena (Krashia et al., 2019; Limanaqi et al., 2020b). They are long-projecting neurons with poorly or unmyelinated axons endowed with multiple varicosities that provide profuse synaptic innervations within various brain areas where the behavioral effects of METH are eventually produced. Again, their autonomous pacemaker activity implies high-energy requirements and sustained mitochondrial function. Thus, efficient mechanisms of axonal transport and protein quality control are needed to replace damaged mitochondria and synaptic components. Within this scenario, autophagy holds center stage by operating promiscuously with the proteasome and endocytic/secretory pathways at both synapses and cell bodies. In fact, autophagy regulates DA release and activity (Hernandez et al., 2012; Hunn et al., 2019), and in turn, catecholamine-containing neurons are inherently susceptible to degeneration associated with an autophagy failure (Castino et al., 2008; Du et al., 2017; He et al., 2018; Lazzeri et al., 2018; Sato et al., 2018; Wei et al., 2016; Xie et al., 2018). A basis for the high vulnerability of catecholamine-containing neurons to oxidative stress-related damage stems from the reactive nature of DA. In this frame, rescuing autophagy is crucial to promote survival (Guo et al., 2018; Hu et al., 2017; Lazzeri et al., 2018; Li et al., 2017; Wei et al., 2016). This is not surprising since DA-related oxidative/inflammatory events and the build-up of oxidized/misfolded substrates which are

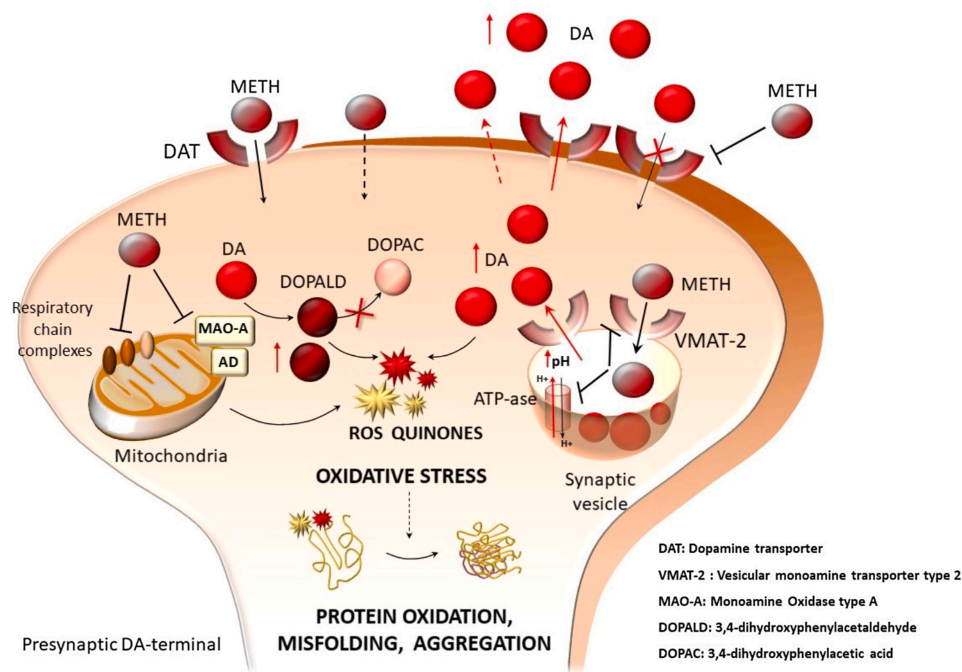


Fig. 2. Molecular targets of METH within DA neurons. METH enters DA terminals via either DAT or passive diffusion. Within DA-storing synaptic vesicles, METH acts as a weak base to disrupt the proton gradient and rise the acidic compartment towards basic values, and it directly inhibits VMAT-2 while displacing VMAT-2 molecular complex from synaptic vesicle membranes to non-canonical membranous compartments. This makes nonpolar DA freely diffusible out of the vesicles thus altering the compartmentalized physiological oxidative deamination of DA, which leads to DA self-oxidation and production of reactive DA by-products (Quinones). Such an effect is exacerbated by METH-induced inhibition of the MAO-A enzyme on the outer mitochondrial membrane. This may also include the uncoupling between MAO-A and aldehyde dehydrogenase (AD), which occludes the conversion of the highly reactive by-product of DA oxidation DOPALD into the quite inert DOPAC. Accumulation of DOPALD potentiates the production of reactive DA by-products. At the same time, METH impairs mitochondrial respiratory chain complexes, to produce mitochondrial dysfunctions and subsequent intracellular accumulation of reactive oxygen species (ROS) adding to DA-related oxidative stress and altered proteostasis within DA terminals. At the same time, cytosolic presynaptic DA diffuses in the extracellular space either by passive diffusion or via the reverted direction of DAT. In detail, METH impairs DAT activity either via direct inhibition or via reverting its direction, which potentiates the accumulation of freely diffusible DA in the extracellular space.

induced by METH (such as alpha-synuclein, tau, and prion protein), may converge to impairing the autophagy machinery; in turn, impaired autophagy may fuel synaptic alterations, accumulation of toxic protein aggregates, and neurodegeneration (Da Luz et al., 2015; Feng et al., 2020; Ferrucci et al., 2017; Fornai et al., 2006; He et al., 2018; Li et al., 2017; Martinez-Vicente et al., 2008; Muñoz et al., 2012; Silva et al., 2020; Song et al., 2014). As we shall see, despite increasing the number of autophagy markers and vacuoles, METH produces DA-related oxidative damage of mitochondria and proteins, which may eventually converge to engulfing autophagy compartments while impeding autophagy flux. Recent insights on the mechanisms of action of METH suggest that such a drug of abuse may early affect the autophagy machinery by impairing the recruitment of key components that are required for autophagosome formation and maturation (Lazzeri et al., 2018).

Considering the role of autophagy in the modulation of DA-related behavior, this appears as a key for METH-induced behavioral sensitization beyond neurotoxicity. Autophagy is also key to preventing neuroinflammation and disruption of the blood-brain-barrier, which is bound to the early effects of DA-related METH administration. This anticipates the impressive overlap between the effects of METH and autophagy impairment upon DA system alterations, casting the hypothesis that autophagy dysfunction in drug abuse may bridge psychiatric manifestations and neurodegenerative phenomena.

3. The autophagy machinery: bridging cell-clearance and synaptic plasticity

Macroautophagy (here referred to as autophagy) is a phylogenetically conserved eukaryotic cell-clearing system that plays a seminal role in cell homeostasis (Rubinsztein et al., 2015; Tooze and Schiavo, 2008). Autophagy starts with a double-membrane nascent vacuole called phagophore, where sequestration of various cellular substrates occurs. These encompass lipids, sugars, nucleic acids, proteins, and even whole organelles or cell-compartments. The autophagy-dependent clearance of specific organelles such as mitochondria, pathogens, ribosomes, portions of the endoplasmic reticulum, or synaptic vesicles, is conventionally designated as mitophagy, xenophagy, reticulophagy, or vesiculophagy, respectively (Binotti et al., 2014; Okamoto, 2014; Rubinsztein et al., 2015). The sequestration of substrates within the sealing phagophore may either occur as a "bulk" process or involve adaptor/receptor proteins such as SQSTM1/p62 and optineurin. While shuttling ubiquitinated cargoes to the forming autophagosome, these proteins are themselves degraded by autophagy, thus serving as markers of autophagy progression (Okamoto, 2014; Rubinsztein et al., 2015a). Once mature, the autophagosome may fuse either directly with the lysosome to produce the autolysosome, or with endomembrane vesicles (multivesicular bodies), giving birth to the amphisome (Fader and Colombo, 2009). The latter eventually merges with the lysosome to complete substrates' breakdown while some metabolic by-products are recycled.

Autophagy progression, starting from the biogenesis and maturation of autophagosomes up to the fusion with lysosomes, is finely orchestrated by a complex machine system that consists of more than 30 autophagy-related-gene (Atg) products (Xie and Klionsky, 2007; Yu et al., 2018). A crucial step in autophagy activation consists of the conversion of Atg8 (LC3 in mammals) into LC3I, lipidation of LC3I into LC3II isoform, and the incorporation of LC3II into the phagophore membrane. This is a key step for the vacuole to expand and seal, and for cytoplasmic elements to be properly engulfed. As LC3-II is quite specifically associated with autophagosomes and autolysosomes, it is widely employed as a marker for monitoring autophagy at the morphological, ultrastructural, and biochemical levels. However, an increase in LC3-II levels is not sufficient to draw sound conclusions on the autophagy status, since it may indicate either an increase or a decrease of the autophagy flux. This is magnified when semi-quantitative techniques are employed, such as LC3-positive puncta quantification, which is considered as a gold-standard assay for assessing the numbers of autophagosomes in cells (Runwal et al., 2019). In

fact, endogenous LC3-positive puncta do occur and become even larger in cells where autophagy induction and LC3-II formation are abrogated (Runwal et al., 2019). This may be due to either LC3-I sequestration to p62-positive aggregates that accumulate when autophagy is impaired, or misplacement of LC3 from autophagy vacuoles to the cytosol (Lazzeri et al., 2018; Runwal et al., 2019). This may lead to results misinterpretation unless LC3 assessment is coupled with other autophagy markers, autophagy flux assays, or ultrastructural immune-labeling (Lazzeri et al., 2018). As we shall see, this is key in the case of METH, whereby early autophagy impairment occurs despite the production of massive LC3 fluorescent signal (Castino et al., 2008; Lazzeri et al., 2018).

Besides LC3, other autophagy proteins ranging from Atg3 to Atg7, as well as the adaptor protein SQSTM1/p62 are widely employed as markers for monitoring autophagy. In fact, they are key in autophagy progression, and also contribute to the processing and conjugation of Atg8/LC3 to the growing autophagosome membrane lipids (Xie and Klionsky, 2007; Yu et al., 2018). For instance, Atg7 participates in LC3 lipidation by directly activating Atg8/LC3 meanwhile promoting its transfer to the E2 enzyme Atg3. At the same time, Atg7 binds to Atg12 fostering its binding to Atg5, which leads to the formation of the Atg12-Atg5 conjugate complex (Tooze and Schiavo, 2008). After recruiting Atg16, such a complex localizes to the expanding phagophore, where it acts as an E3 ligase fostering the final transfer of Atg8 to its lipid target phosphatidylethanolamine (PE). Several biochemical pathways that are placed upstream of the autophagy machinery finely tune its activity by regulating Atg products. The best-known pathway consists of mTOR complex1 (mTORC1) which hampers autophagy induction through phosphorylation of Atg13 and subsequent inhibition of Atg1 (ULK1 in mammals) (Kamada et al., 2010). The mTOR complex represents a downstream substrate of the PI3K/PTEN/Akt pathway, which conveys extracellular and environmental stimuli to orchestrate cell growth, proliferation, metabolism, and autophagy initiation in response to bioenergetics and nutritional requests (Zoncu et al., 2011). The binding of insulin and growth factors promotes Akt/mTOR activity, which, in turn, promotes protein synthesis, along with ribosome, and lipid biogenesis meanwhile inhibiting autophagy (Ma and Blenis, 2009). Conversely, the gold-standard mTORC1 inhibitor rapamycin complexes with the FK506-binding protein 12 (FKBP12) of TOR to induce autophagy. Additional pathways that foster autophagy initiation consist of the activation of 5′ AMP-activated Protein Kinase (AMPK) or inhibition of Glycogen Synthase Kinase 3 Beta (GSK3-β) (Fornai et al., 2008; Pasquali et al., 2010; Weikel et al., 2016). Again, activation of the transcription factor EB (TFEB) promotes autophagy induction by acting either in cooperation with or independently of mTORC1 to regulate lysosomal activation and autophagosome-lysosome fusion (Settembre et al., 2012; Zhou et al., 2013a, b). Again, activation of the NAD-dependent deacetylase Sirtuin-1 (SIRT1) promotes autophagy via de-acetylation of Atg5, Atg7, LC3 and activation of the transcription factor forkhead box O3 (FOXO3) (Pietrocola et al., 2012). The latter controls the expression of mTOR and several pro-autophagic proteins.

Similar to stressful events, abused substances produce compensatory or maladaptive plastic changes that occur along with alterations of protein quality control at the synapses (Limanaqi et al., 2020b). These alterations are bound to intracellular stress-related pathways that are known to promptly recruit the autophagy machinery in the attempt to restore neuronal homeostasis. These include oxidative and ER stress, the unfolded protein response (UPR), and para-inflammation. However, prolonged stress/drug abuse may hamper the neuronal attempt to clear via increased autophagy. This may promote disease through a vicious cycle of synaptic alterations spreading to axons, cell bodies, and trans-synaptically, to neighboring cells. As a proof of concept, autophagy is commonly dysregulated in a plethora of CNS disorders where a feedback loop establishes between impaired proteostasis, and oxidative/inflammatory events to foster synaptic alterations up to neuronal cell loss (Feng et al., 2020; Hara et al., 2006; Hu et al., 2017; Hui and Tanaka, 2019; Komatsu et al., 2006, 2007; Limanaqi et al., 2018a; Pigulevskiy et al., 2020; Ryskalin et al., 2018; Sato et al., 2018; Shehata et al., 2018; Sumitomo et al., 2018a). In fact, genetically inactivating autophagy in murine models reproduces both psychiatric alterations and key features of neurodegeneration; rescuing autophagy improves behavior and provides neuroprotection instead (Feng et al., 2020; Hara et al., 2006; Hu et al., 2017; Hui and Tanaka, 2019; Komatsu et al., 2006, 2007; Limanaqi et al., 2018a; Merenlender-Wagner et al., 2014; Pigulevskiy et al., 2020; Ryskalin et al., 2018; Sato et al., 2018; Shehata et al., 2018; Sumitomo et al., 2018b).

Bridging autophagy deficits and neuropsychiatric conditions, recent studies unraveled a link between synaptic autophagy, synaptic plasticity, modulation of behavior, and emotional/cognitive experience (Tomoda et al., 2020). Behavioral alterations in autophagy-deficient models are bound to an abnormal expression of synaptic proteins, which leads to structural changes at the presynaptic active zone and enhanced neurotransmitter release (Gupta et al., 2016). Conversely, rescuing autophagy/lysosomal protein degradation prevents early synaptic alterations and improves behavioral deficits in several experimental models of aging, neurodegeneration, as well as cognitive and affective disorders (De Risi et al., 2020; Gupta et al., 2016; Masini et al., 2018; Merenlender-Wagner et al., 2014; Puri and Subramanyam, 2019; Tomoda et al., 2020; Vartak et al., 2019; Xiao et al., 2015). These effects are lost when autophagy is inhibited pharmacologically, or genetically through deletion of *Atg7* and *Atg8* (De Risi et al., 2020; Gupta et al., 2016; Merenlender-Wagner et al., 2014).

Altogether, these findings suggest that autophagy impairment may be an early event in neurodegeneration; thus rescuing autophagy/lysosomal degradation can counteract early synaptic dysfunctions that may precede neurodegeneration (Birdsall and Waites, 2019; Lee and Kim, 2019). This is further supported by the plastic and neuroprotective effects of autophagy-inducing compounds, such as mTOR and GSK3-β inhibitors (Ali et al., 2020; Gassen et al., 2014, 2015; Gassen and Rein, 2019; Gulbins et al., 2018; Kara et al., 2018, 2013; Kim et al., 2018; Masini et al., 2018; Merenlender-Wagner et al., 2014; Zhang et al., 2007; Ryskalin et al., 2018). This also fits with evidence that various psychostimulants and abused substances activate mTOR and GSK3- β in the mesostriatal and mesocorticolimbic circuitry, while their inhibition through rapamycin and lithium, respectively, reverses psychostimulant-induced sensitization, relapse, reinforcement, and toxicity (Barak et al., 2013; Beckley et al., 2016; Dayas et al., 2012; Huang et al., 2018; Lazzeri et al., 2018; Lee et al., 1999; Li et al., 2017; Mehrafza et al., 2019; Neasta et al., 2014; Xu et al., 2011; Yan et al., 2019). At the molecular level, this is evident by the reversal in METH-induced increase in spine density, as well as Fos and CREB expressions in the striatum, prefrontal cortex, and amygdala of murine models (Huang et al., 2018; Lee et al., 1999; Mehrafza et al., 2019). A graphical summary of the autophagy pathway, along with the specific autophagy steps targeted by METH is provided in Fig. 3.

3.1. Autophagy modifies synaptic events implicated in METH addiction

Various synaptic events that may occur in substance use disorders (SUD), including METH-induced addiction, are bound to autophagy alterations. These include:

i) *Oxidative-related accumulation of substrates promoting synaptic dysfunctions and autophagy blockade.*

The build-up of altered mitochondria and oxidized/altered proteins which are implicated in the effects of METH may overwhelm autophagy capacity to produce early synaptic dysfunctions and neurotoxicity (Atkin et al., 2012; Da Luz et al., 2015; Feng et al., 2020; He et al., 2018; Muñoz et al., 2012; Polajnar and Žerovnik, 2014). These include alpha-synuclein, tau, prion protein, and DISC-1. Inducing autophagy is key to counteracting the accumulation of damaged mitochondria and the abovementioned proteins, thus preventing both synaptic alterations and neurotoxicity (Decressac et al., 2013; Fang et al., 2019; Han et al.,

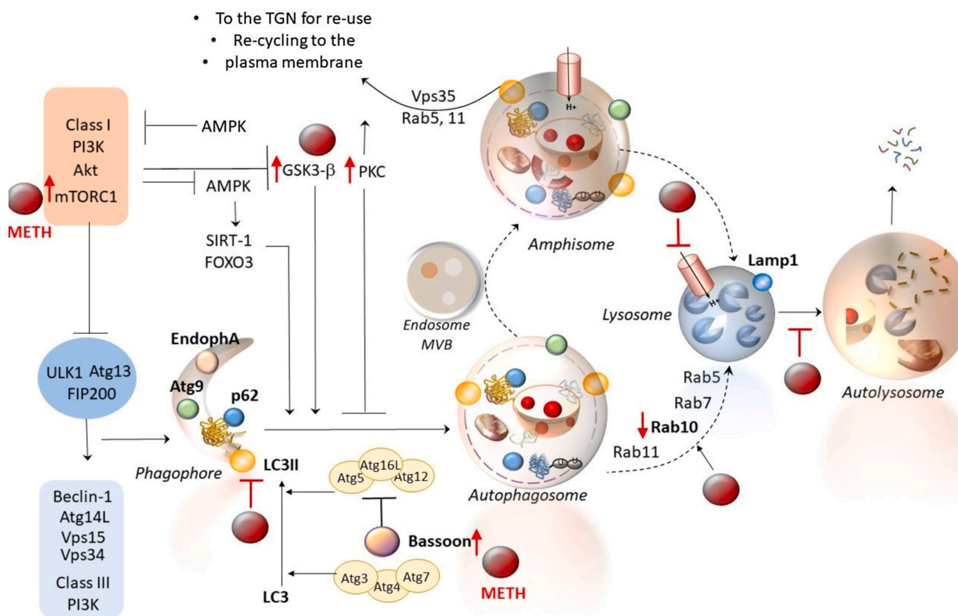


Fig. 3. Overview of the autophagy pathway and autophagy steps targeted by METH. Autophagy initiation is governed by the Class I PI3K/Akt pathway through activation of mammalian Target of Rapamycin (mTOR), which in turn inhibits autophagy via inactivation of the ULK1/Atg13, FIP200 complex. Again, the Class I PI3K/Akt pathway hampers autophagy initiation and progression through inhibition of the 5′ AMP-activated Protein Kinase (AMPK), and its downstream factors Sirtuin-1 (SIRT1) and factor forkhead box O3 (FOXO3). On the other hand, the Class I PI3K/Akt pathway may promote autophagy through inhibition of Glycogen Synthase Kinase 3 Beta (GSK3-β). Autophagy initiation and progression requires the Class III PIK3 complex that is composed of Beclin-1/Vps34/Vps15/Atg14. This participates in the phagophore incorporation of Atg proteins such as EndophilinA, Atg9, and LC3 (Atg8). Several additional Atg proteins ranging from Atg3 to Atg16 L participate in the conversion of LC3 into soluble LC3I, ubiquitination-like enzymatic lipidation of LC3I to form lipid-bound LC3II isoform, and the incorporation of LC3II into the phagophore membrane. On the other hand, specific proteins such as Bassoon impair LC3II formation and the incorporation of LC3II into the phagophore membrane. Once mature, the autophagosome merges either directly with the lysosome, or with endosomes and multivesicular bodies (MVB) giving birth to the amphisome. The latter fuses with the lysosome, where cargo degradation eventually occurs. Several endosomal Rab proteins ranging from Rab5 to Rab 11 are key for both autophagosome maturation and fusion of autophagosomes with lysosomes. Rab proteins, in cooperation with the VPS35 retromer, are also key for sorting endosomal/autophagy proteins and substrates to the trans-Golgi network for re-use and recycling to the plasma membrane. METH impairs autophagy at several levels, including i) hyperactivation of mTOR, GSK3-β, and protein kinase C (PKC), ii) hampering of LC3II formation and incorporation into the autophagosome, which may be bound to Bassoon upregulation, iii) downregulation of Rab10, iv) impairment of vesicle acidification and fusion of autophagosomes with lysosomes.

2020; Limanaqi et al., 2020a; Palikaras and Tavernarakis, 2020; Polito et al., 2014). Recent studies underscore the pivotal contribution of mitophagy in synaptic function beyond neuropathology (Palikaras and Tavernarakis, 2020).

Mitochondrial damage, and mitophagy dysregulations have been implicated in synaptic alterations underlying the development and progression of mental and neurodegenerative diseases (Manji et al., 2012; Palikaras and Tavernarakis, 2020; Toker and Agam, 2015). In line with this, promoting mitophagy improves both behavioral alterations and neuropathology in various experimental models (Fang et al., 2019; Han et al., 2020; Palikaras and Tavernarakis, 2020; Toker and Agam, 2015). The key role of mitophagy in neurodegeneration is best exemplified by PD, whereby mutations in *PINK1* abrogate autophagy-dependent removal of impaired mitochondria upstream of the Parkin protein (Geisler et al., 2010a). In addition to compromised PINK1 kinase activity, reduced binding of PINK1 to Parkin leads to failure in Parkin mitochondrial translocation. This, in turn, leads to impaired mitophagy and accumulation of damaged mitochondria, which may contribute to disease pathogenesis. Also, Parkin pathogenic mutations may interfere with distinct steps of mitochondrial translocation, ubiquitylation, and final clearance through p62/SQSTM1-related mitophagy (Geisler et al., 2010b).

Generation of superoxide radicals, mitochondrial damage, and impaired mitophagy are key events in the effects produced by METH (Cadet et al., 1994; Jayanthi et al., 2001, 2004; Wu et al., 2007; Lenzi et al., 2012; Ruan et al., 2020). The GSK3-β inhibitor, and autophagy inducer lithium is key to promote protective mitophagy (Fornai et al., 2008; Natale et al., 2015), meanwhile counteracting various events that are bound to METH-induced mitochondrial alterations. These include reduction of mitochondrial Cytochrome c levels, an increase of anti-apoptotic Bcl-2/Bax ratio, and alleviation of the respiratory chain complex activity impairment induced by METH (Bachmann et al., 2009; Feier et al., 2013). Sub-cellular evidence in METH-treated cells has been provided that the mitophagy-related protein PINK1 is a key for METH-induced alterations in mitochondrial morphology and number. Reminiscent of what occurs in PD, METH induces marked accumulation of dysfunctional mitochondria in the absence of functional PINK1 and upon autophagy alterations (Lenzi et al., 2012). This is not surprising since autophagy induction through either mTOR or GSK3-β inhibition is seminal to maintain mitochondrial homeostasis by orchestrating mitophagy and the biogenesis of novel mitochondria (mitochondriogenesis) (Ferese et al., 2020; Natale et al., 2015). This occurs in cooperation with molecules such as PGC-1α, NRF-2, and TFAM. While LC3 along with the adaptor proteins p62, Parkin, and PINK-1 polarize within altered mitochondria to promote mitophagy, Nrf2, PGC-1α, and TFAM contribute to shuttling the signal from mitophagy-prone altered mitochondria towards the nucleus to induce mitochondrial biogenesis (Ferese et al., 2020). Remarkably, PGC-1α, NRF, and TFAM are markedly reduced by repeated METH administration in experimental animals (Beirami et al., 2018). Again, within DA cell lines, METH-induced oxidative stress and mitochondrial damage are accompanied by impaired mitochondriogenesis (Wu et al., 2007). This suggests that METH-related autophagy alterations may impair mitophagy and mitochondriogenesis, which calls for further studies in METH models linking autophagy and defects in mitochondrial dynamics.

ii) *Altered DA release and excitatory-inhibitory activity in the brain*

Autophagy plays a direct role in DA release and re-uptake (Hernandez and Sulzer, 2012; Hunn et al., 2019). In detail, impairment of autophagy at the synapse leads to unrestrained DA release, as documented in mice lacking *Atg7* specifically within DA neurons. These animals display increased evoked striatal DA secretion along with decreased DA re-uptake (Hernandez et al., 2012; Hunn et al., 2019). Conversely, activated autophagy following mTOR inhibition, as confirmed at the ultrastructural level, degrades DA-filled synaptic

vesicles to decrease evoked DA release in wild-type but not transgenic mice (Hernandez et al., 2012).

Abnormal DA release induced by abused psychostimulants, including METH, is also bound to a decreased inhibitory GABA input onto DA and GLUT neurons (Centonze et al., 2002; Jiao et al., 2015). Downregulation of GABA signaling within the mesolimbic, mesocortical, and cortico-striatal pathways is implicated in the development of SUD (Centonze et al., 2002; Jiao et al., 2015; Zhang et al., 2006). In detail, METH-induced behavioral sensitization is associated with down-regulation of the $GABA_A$ α2 receptor subunit and impaired striatal GABA transmission (Zhang et al., 2006). In this frame, it is remarkable that autophagy balances excitatory-inhibitory activity in the brain by orchestrating the clustering of $GABA_A$ receptors on the plasma membrane (Hui and Tanaka, 2019; Sumitomo et al., 2018a). In *Ulk2+/-* mice, similar to mice bearing a conditional deletion of autophagy within GABA-ergic MSNs neurons, behavioral abnormalities occur, such as social deficits, increased distress, and anxiety, along with cognitive alterations (Hui and Tanaka, 2019; Sumitomo et al., 2018a; Pigulevskiy et al., 2020). These abnormalities are associated with the entrapment of $GABA_A$ receptors within p62-positive aggregates that are reminiscent of stagnant autophagy vacuoles, as well as impaired degradation of the inwardly-rectifying potassium channel KCNJ/Kir2 (Hui and Tanaka, 2019; Sumitomo et al., 2018a; Pigulevskiy et al., 2020). Conversely, autophagy activation fosters the distribution of $GABA_A$ receptors on the plasma membrane. This is associated with the reinstatement of excitatory-inhibitory balance and reversal of behavioral abnormalities (Hui and Tanaka, 2019; Sumitomo et al., 2018a).

iii) *Abnormal stimulation of DA and GLUT receptors*

Abnormal DA and GLUT transmissions play a synergistic role in the development of METH psychosis and addiction through convergent activation of striatal intracellular signaling pathways that are placed downstream of DA and GLUT receptors (Miyazaki et al., 2013). Remarkably, autophagy impairment at synapses may occur following abnormal stimulation of DA receptors (Wang et al., 2018; Yang et al., 2020a, b). In detail, D1-like DA receptors (D1DR and D5DR), which are mostly implicated in METH-induced addiction and neurotoxicity, inhibit autophagy initiation and flux. This occurs through Ca^{2+} overload-dependent activation of the phospholipase C/inositol trisphosphate (PLC/IP3) pathway, and mTOR-dependent mechanisms (Wang et al., 2018; Yang et al., 2020a, b). On the other hand, D2-like DA receptors (D2D3, D3DR, D4DR) promote autophagy induction and flux through BECN1-dependent pathways and preservation of protein synthesis (Barroso-Chinea et al., 2020; Dolma et al., 2016; Wang et al., 2015, 2018). Abnormal stimulation of D2-like DA receptors is also involved in the sensitizing and neurotoxic effects of METH, as shown in mice models of DRD2 inactivation (Ares-Santos et al., 2013; Moratalla et al., 2017; Solís et al., 2019). However, these effects may be also related to presynaptic DRs that play an inhibitory role in METH-induced potentiation of DA release. A reduction in D2-/D3DRs levels is documented in the striata and orbitofrontal cortex of chronic METH abusers, which may explain the decreased sensitivity to natural rewards and the compulsive drug use as a means to temporarily compensate for this deficit (Lee et al., 2009; Volkow et al., 2001, 2010b). The opposite effects of DR subtypes upon autophagy activity suggest that long-term, abnormal activation of D1-like DA receptors, coupled with a progressive reduction of D2-like DA receptors may converge to impairing autophagy at DA postsynaptic brain regions, which may be key to sustain METH addiction. This is supported by evidence that various psychostimulants activate mTOR and GSK3-β in the striatal and limbic brain areas, while inhibition of mTORC1 and GSK3-β reverses psychostimulant-induced sensitization, relapse, and reinforcement (Barak et al., 2013; Beckley et al., 2016; Dayas et al., 2012; Huang et al., 2018; Lazzeri et al., 2018; Lee et al., 1999; Lai et al., 2018; Mehrafza et al., 2019; Neasta et al., 2014; Xu et al., 2011; Yan et al., 2019). However, the role of autophagy in this frame remains to be specifically investigated. Another controversial, yet intriguing issue to be clarified is the role of D3DRs. Several reports suggest that abnormal stimulation and expression of D3DRs is implicated in METH-induced sensitization, as postulated for some psychiatric diseases as well (Leriche et al., 2004; Sokoloff et al., 2006; Zhu et al., 2012; Choi et al., 2018). This is intriguing if one considers recent evidence indicating D3DR as the main D2-like receptor subtype that promotes autophagy induction through mTORC1 inhibition (Barroso-Chinea et al., 2020). However, it is worth mentioning that this may also involve D1DRs that are known to inhibit autophagy instead, as chronic stimulation of D3DRs amplifies D1DR-induced Adenylate Cyclase (AC) signaling (Fiorentini et al., 2008; Maggio et al., 2009). In fact, D1DRs and D3DRs co-localize in a large number of neurons throughout the striatum, where they form heterodimers (Fiorentini et al., 2008). In the presence of D3DRs, DA stimulates D1DRs with higher potency. Again, hetero-dimerization with D3DRs abolishes D1DRs internalization and enables the internalization of D1/D3-DR complex through a mechanism involving β-arrestin (Fiorentini et al., 2008). Since both autophagy and proteasome systems are implicated in β-arrestin-dependent receptor internalization, it is likely that following METH-induced DA overload, impairment of cell-clearing pathways occludes the internalization of the D1-/D3DR complex (Limanaqi et al., 2019). This is expected to stimulate the D1DR-AC pathway with higher potency, which may, in turn, contribute to METH-induced behavioral sensitization.

Rescuing autophagy is also key to preventing abnormal stimulation of GLUT receptors and subsequent Ca_{2+}-related excitotoxic cascades, which are bound to the effects of METH (Scheyer et al., 2016; Battaglia et al., 2002a, b; Kulbe et al., 2014; Shehata et al., 2018, 2012). This occurs through the internalization and desensitization of AMPAR (Kulbe et al., 2014; Shehata et al., 2018, 2012). This was documented in mice models of post-traumatic stress disorder, where autophagy induction, through AMPAR endocytosis and degradation, contributes to erasing and overcoming reconsolidation-resistant fear memory (Shehata et al., 2018). This is key in the case of METH addiction since enhanced expression and activity of AMPAR in the ventral striatum contributes to the incubation of METH craving (Scheyer et al., 2016).

iv) *Altered expression of endocytic synaptic proteins interacting with autophagy.*

Alterations (mutations, overexpression, dysfunctions) of canonical synaptic proteins occurring in SUD aside from certain psychiatric and neurodegenerative disorders, contribute to impairing synaptic autophagy. These include Bassoon, Endophilin-A, Rab GTPases, DISC1, and the VPS35 retromer (Atkin et al., 2012; Bosch et al., 2015; Brodin and Shupliakov, 2018; Lee and Kim, 2019; Limanaqi et al., 2018a; Okerlund et al., 2018; Tomoda et al., 2020; Vijayan and Verstreken, 2017).

Bassoon is a presynaptic scaffolding protein within the active zone, which limits synaptic autophagy via binding to Atg5 and hampering of Atg5−12 complex formation (Fig. 3, Okerlund et al., 2018). Conversely, Bassoon downregulation promotes synaptic autophagy and degradation of synaptic vesicles through the fusion of bouton-derived autophagosomes with lysosomes (Okerlund et al., 2018). Remarkably, Bassoon expression is up-regulated in the brain of amphetamine-sensitized animals (Bosch et al., 2015), and it is mutated in patients with dementia and neurodegeneration (Yabe et al., 2018). At present, the link between Bassoon-related catabolic synaptic processes and specific brain disorders remains to be investigated. However, it is conceivable that early synaptic insults altering the function of specific synaptic proteins that are, in turn, bound to autophagy progression, might foster deficits in synaptic transmission. This may promote synaptic loss up to neuronal degeneration.

EndophilinA is a synapse-enriched protein implicated in the stimulation of both synaptic autophagy, and synaptic vesicle cycle through coordination of neurosecretory vesicle priming, fusion, and endocytosis (Gowrisankaran et al., 2020; Soukup et al., 2016). In fact, EndophilinA induces the formation of highly curved membranes, which also serve as docking stations for autophagy factors (Fig. 3, Soukup et al., 2016). EndophilinA is downregulated by METH (Bosch et al., 2015) and its

dysfunctions, are accompanied by autophagy impairment, which accelerates activity-induced neurodegeneration, as it occurs in PD (Murdoch et al., 2016; Soukup et al., 2016; Limanaqi et al., 2018a).

Again, dysfunctional or mutated Rab-GTPases (e.g. Rab4, 5, 10, and 11) impair both synaptic vesicle recycling and autophagy, since they are involved in phagophore formation, autophagosome maturation, and fusion with the lysosomes (Fig. 3, Binotti et al., 2016; Palmisano et al., 2017; Stenmark, 2009; Szatmári et al., 2014). METH directly downregulates Rab10 (Vanderwerf et al., 2015), the activation of which is essential for both LC3 recruitment to the autophagosome and fusion of autophagosomes with lysosomes (Li et al., 2016). In fact, downregulation of RAB-10 impairs autophagy flux, as evident by the loss of co-localization between lysosome and autophagosome reporters (Li et al., 2016; Palmisano et al., 2017). Again, while impairing autophagy, dysfunctions of Rab5 and Rab11 alter the trafficking and recycling of DAT to the plasma membrane, which is reminiscent of the mechanism of action of METH (Furman et al., 2009; Hong and Amara, 2013; Loder and Melikian, 2003). In the light of an interdependency that exists between autophagy and endocytic trafficking pathways, it is conceivable that autophagy dysregulation may be involved in METH-induced alterations of DAT trafficking. In fact, similar to abused drugs, endocytic molecular events which impair DAT activity, trafficking, and recycling, do affect autophagy progression (Furman et al., 2009; Hong and Amara, 2013; Lin et al., 2012; Loder and Melikian, 2003; Tang et al., 2015; Wu et al., 2017; Zavodszky et al., 2014). Besides alterations/mutations of the endocytic proteins Rab5, and Rab11, these include abnormal activation of PKC, and impairment of the VPS35 retromer (Furman et al., 2009; Hong and Amara, 2013; Lin et al., 2012; Loder and Melikian, 2003; Tang et al., 2015; Wu et al., 2017; Zavodszky et al., 2014). PKC is involved in METH-induced addiction, memory impairment, and mania-like behavior, and remarkably, in METH-induced impairment of both autophagy and proteasome (Lin et al., 2012; Narita et al., 2004; Valvassori et al., 2020). PKC is directly bound to METH-induced DAT internalization, and decrease of DAT surface availability, as well as potentiation of synaptic DA release via both DAT phosphorylation and downregulation of presynaptic D2DR auto-receptors (Lin et al., 2012; Loder and Melikian, 2003; Luderman et al., 2015; Shin et al., 2019).

Considering recent evidence that implies synapses as sites of early pathology in neuropsychiatric disorders, a potential role of synaptic retromer-autophagy dysfunction in disease initiation is emerging (Brodin and Shupliakov, 2018). The retromer pathway is bound to both autophagy progression and the endocytic trafficking and processing of potentially harmful, misfold-prone proteins, such as alpha-synuclein, and tau (Brodin and Shupliakov, 2018; Tang et al., 2015; Wen et al., 2011; Zavodszky et al., 2014). Within DA neurons, the retromer guarantees the correct trafficking and recycling of both Atg9 and Lamp2 proteins to orchestrate autophagy induction and progression (Tang et al., 2015; Zavodszky et al., 2014). Again, both Atg9 and the retromer are required for the formation, maturation, and compartmentalized acidification of endosomal, synaptic, and autophagy-lysosomal vacuoles, which instead is erased by METH (Bader et al., 2015; Limanaqi et al., 2018a; Tallóczy et al., 2008). Intriguingly, the effects of VPS35 retromer dysfunction are also reminiscent of those produced by METH. Deletion/mutations of VPS35 retromer impairs autophagy/lysosomal pathway while producing memory deficits, defective long-term potentiation, and altered proteostasis, up to PD-like neuropathological changes (Tang et al., 2015; Wen et al., 2011; Zavodszky et al., 2014). These effects are associated with endosome perturbations, dysfunctional autophagy, and aberrant lysosomes. Again, VPS35 retromer dysfunctions are associated with altered DA outflow, increased DA turnover, decreased DAT availability at the plasma membrane, as well as dystrophic DA neurites/axons and behavioral alterations (Cataldi et al., 2018; Vanan et al., 2020; Zavodszky et al., 2014). In fact, in DA nerve terminals and cell bodies, the depletion of VPS35 retromer disrupts both autophagy and DAT and VMAT-2 recycling to the plasma membrane and synaptic vesicles, respectively (Wu et al., 2016, 2017). Within the synapse, the retromer, in cooperation with endocytic Rabs, also recycles neurotransmitter receptors including AMPAR, and D1DR (Tian et al., 2015; Wang et al., 2016; Zhang et al., 2012). This remarks quite impressively the interdependency between synaptic homeostasis, autophagy, and DA neurotransmission (Fig. 4), which provides a clue for investigating the role of synaptic and Rab proteins and the VPS35 retromer in models of METH administration and drug addiction.

It is worth mentioning that besides macroautophagy, two other forms of autophagy exist, namely microautophagy (MIC), and chaperone-mediated autophagy (CMA), which similarly converge at the level of lysosomes (Okamoto, 2014). During MIC, cytoplasmic proteins are degraded either by direct transport into lysosomes through invaginations of the lysosomal membrane, or via Hsc70-mediated delivery of proteins into late endosomes fusing with lysosomes (Sahu et al., 2011; Uytterhoeven et al., 2015). The Hsc70 chaperone is also involved in CMA, whereby it recognizes proteins with a specific amino acid motif and associates with the lysosomal membrane protein Lamp2A to translocate proteins into the lysosome (Kaushik and Cuervo, 2012). Lamp2A acts as the rate-limiting step for the activity of the CMA pathway (Kaushik and Cuervo, 2012). Similar to autophagy, an age-related decline occurs in CMA function, which is associated with reduced levels of Lamp2A in various models of neurodegeneration (Cuervo and Wong, 2014). Again, similar to what is reported for autophagy, CMA is impaired by METH, and it appears seminal for the survival of DA neurons (Sun et al., 2019). Silencing of *LAMP2A* in DA neurons is accompanied by the occurrence of PD-like motor deficits, neuronal protein inclusions, accumulation of autophagy vacuoles, neuro-inflammation, and progressive neurodegeneration (Xilouri et al., 2016). CMA activity can be impaired by oxidized protein adducts such as DA-modified α-syn, providing a potential explanation for the high susceptibility of catecholamine nuclei (Martinez-Vicente et al., 2008).

Remarkably, Hsc70 is enriched presynaptically where it promotes membrane curve to activate MIC/CMA-related synaptic protein turnover, meanwhile promoting neurotransmitter release (Uytterhoeven et al., 2015). Within DA neurons, Hsc70 interacts with VMAT-2, aromatic amino acid decarboxylase (AADC), and tyrosine hydroxylase (TH), to promote DA synthesis and DA storage within synaptic vesicles (Parra et al., 2016). Thus, besides autophagy, MIC and CMA also appear key in DA activity and metabolism, which may be relevant for METH-induced addiction. Although the present review is focused on macroautophagy, we wish to point out that an interplay, and often compensatory mechanisms, do occur between the three different forms of autophagy, which deserves to be further investigated in the context of drug abuse, synaptic plasticity, and neurodegeneration.

3.2. *Susceptibility genes for mental disorders bridging DA activity, autophagy alterations, and METH-induced sensitization*

In the frame of synaptic alterations underlying DA-related behavioral sensitization, several susceptibility genes for mental disorders encode for proteins that are bound to both DA neurotransmission and autophagy, configuring as potential targets of METH.

The disrupted in schizophrenia 1 (*DISC1*) gene encodes for the DISC1 protein, which is implicated in neurogenesis, neuronal migration, axon/dendrite, and synapse formation (Brandon and Sawa, 2011). Transient knockdown of DISC1 in pyramidal neurons of the prefrontal cortex during pre- and perinatal stages leads to selective abnormalities in mesocortical DA maturation and behavioral abnormalities associated with disturbed cortical neurocircuitry after puberty (Niwa et al., 2010). At baseline, DISC1 plays a key role in DA neurotransmission and excitatory-inhibitory balance in the brain. Conversely, loss-of-function mutations lead to DISC1 aggregates, which impair both neurotransmission and the autophagy flux by co-recruiting endogenous DISC1 and other synaptic proteins, such as DTNBP1/dysbindin (Atkin et al., 2012; Dahoun et al., 2017). In mice models featuring DISC1 deficiency, METH administration dramatically reduces GABA and potentiates DA release

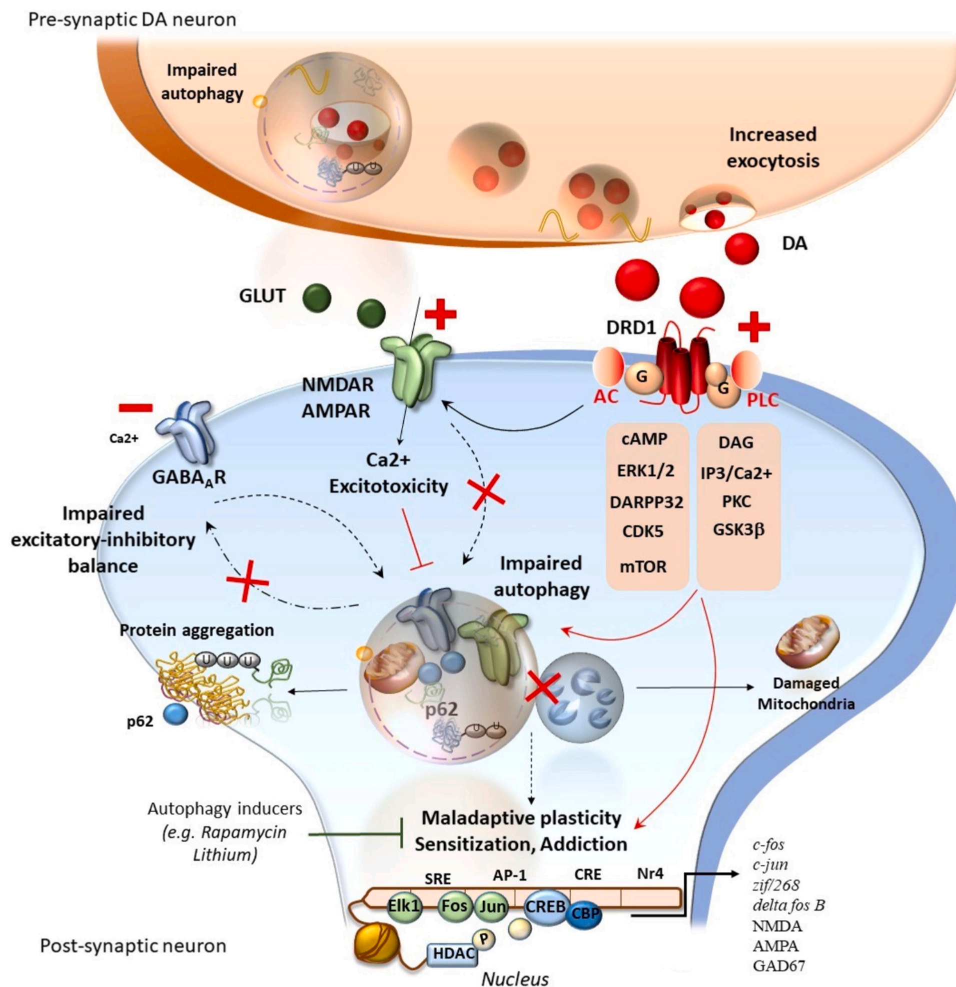


Fig. 4. The effects of METH-induced autophagy impairment within DA presynaptic and post-synaptic neurons. In a way reminiscent of the effects of METH, autophagy impairment at the presynaptic dopamine (DA) terminal induces a hyperdopaminergic state through unrestrained DA release along with decreased DA re-uptake. This leads to abnormal stimulation of type-1 DA receptors (DRD1) that are coupled to adenylate cyclase (AC) and phospholipase C (PLC) pathways, fostering non-canonical biochemical cascades which sustain both METH-induced sensitization and autophagy impairment within postsynaptic neurons. These include cyclic Adenosine Monophosphate (cAMP), phosphorylated ERK1/2, phosphorylated dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP32), cyclin-dependent kinase 5 (CDK5), and mammalian target of rapamycin (mTOR), as well as inositol trisphosphate/Calcium (IP3/Ca2+), protein kinase C (PKC), and glycogen synthase kinase 3 beta (GSK3-β). While contributing to autophagy impairment, these pathways also promote phosphorylation and abnormal activation of glutamate (GLUT) receptors, which in turn, foster Ca2+-related excitotoxicity converging into autophagy flux blockade. In turn, impaired autophagy occludes the degradation of AMPA receptors, meanwhile impairing the membrane availability of $GABA_A$ receptors on the plasma membrane. This impairs excitatory-inhibitory balance, potentially leading to decreased inhibitory GABA input onto DA and GLUT neurons. While contributing to protein aggregation and accumulation of damaged mitochondria, which may aggravate synaptic dysfunctions, these effects converge into epigenetic and transcriptional changes that sustain METH-induced maladaptive plasticity, sensitization, and addiction. This is evident as an increase of transcriptional regulators and early immediate genes, including CREB, c-fos, c-jun, delta FosB, as well as NMDA and AMPA receptors.

while increasing the expression of D1DR in the ventral striatum compared with METH-treated controls (Nakai et al., 2014). Mutations of DISC1 in the striatum are associated with METH-induced behavioral sensitization and abnormal expression of AKT and GSK3-β (Pogorelov et al., 2012). This suggests that DISC1 may bridge alterations in autophagy and DA-related molecular mechanisms that modulate reward and sensitization. DISC1 deficiency may impair autophagy through upregulation of Akt–mTOR pathway, in a way reminiscent of METH-induced abnormal D1DR stimulation (Kim et al., 2009; Zhou et al., 2013a, b). Remarkably, mTOR inhibition reverses the behavioral alterations that are produced by repeated stimulation of D1DR, as well as those occurring in DISC1-deficient and METH-treated mice (Gangarossa et al., 2014; Huang et al., 2018; Zhou et al., 2013a, b). This suggests that disruption of DISC1 activity, including loss-of function-related generation of DISC-1 aggregates, produces behavioral alterations that are bound to an enhanced D1DR-Akt-mTOR signaling, and likely, depressed autophagy (Ryskalin et al., 2018).

An additional susceptibility gene for mental disorders is dihydropyrimidinase-like 2 (*DPYSL2*), which codes for collapsin response mediator protein-2 (CRMP2), a microtubule-associated protein implicated in cytoskeletal dynamics and axonal growth (Liu et al., 2015). Altered CRMP2 levels occur in the brain of mice models exposed to prenatal stress (Lee et al., 2015) and METH (Kobeissy et al., 2008), which is accompanied by increased LC3 levels indicating altered autophagy. Remarkably, the activity of CRMP2 is under the control of two key messengers involved in METH-induced behavioral sensitization, namely cyclin-dependent kinase 5 (CDK5), and GSK3- β (Benavides and Bibb, 2004; Jin et al., 2016; Xu et al., 2011). CDK5 and GSK3- β gene expression and protein levels are bound to METH-related D1DR stimulation, which, at the molecular level, is associated with increased dendritic spine density and tau hyper-phosphorylation (Ferreras et al., 2017; Lebel et al., 2009). In line with this, chronic hyperdopaminergic activity is associated with increased CDK5 signaling and ΔFosB levels in the striatum (Cantrup et al., 2012). Remarkably, besides GSK3- β, which is known to act as an upstream autophagy inhibitor, CDK5 also impairs autophagosome formation by phosphorylating Vps34 and decreasing its activity, thereby leading to impaired PI3P formation (Furuya et al., 2010). This suggests a role for autophagy in CDK5-CRMP2-tau-dependent cytoskeletal alterations and DA transmission in psychiatric behavior. As support, compounds that counteract DA-related behavioral sensitization meanwhile acting as autophagy inducers, downregulate CRMP2 and hyper-phosphorylated tau levels. This is likely to involve inhibition of GSK3-β or CKD5 (Beaulieu et al., 2004, 2009; Cleary et al., 2008; Kara et al., 2013, 2018; Kedracka-Krok et al., 2015; Kim et al., 2017, 2018; Li et al., 2017; Ryskalin et al., 2018; Yan et al., 2019; Zhang et al., 2007). These include lithium, rapamycin, and

antipsychotic drugs such as fluspirilene, trifluoperazine, pimozide, chlorpromazine, sertindole, and clozapine.

In summary, autophagy impairment is bound to synaptic and biochemical events that are produced by METH at both pre-and post-synaptic levels. These include increased extracellular DA activity associated with enhanced DA release and abnormal stimulation of D1DR, decreased DA reuptake, along with impaired GABA release, and abnormal GLUT receptor activity. This suggests that autophagy impairment within the mesolimbic system may contribute to METH-induced behavioral sensitization, mostly through abnormal extracellular DA activity. While altering behavior through a hyperdopaminergic state via enhanced DA release and decreased DA reuptake, autophagy blockade has deleterious effects at both synaptic terminals and cell bodies of DA neurons, driving p62-positive protein aggregation, cellular neuropathology, and cell death (Fig. 5, Hunn et al., 2019). This may extend to post-synaptic neurons as well. In fact, increased expression of p62 and alpha-synuclein occurs in the SNpc and prefrontal cortex of murine models featuring an increased risk of developing psychiatric-like behavior or early-onset PD due to 22q11.2 chromosomal deletions (Sumitomo et al., 2018b). This suggests impaired autophagy, which is likely bound to mTOR hyper-activation. In fact, rapamycin administration in these models reverses both psychiatric- and PD-like signatures at molecular and behavioral levels (Sumitomo et al., 2018b). Thus, autophagy appears seminal for METH-induced behavioral alterations and neurotoxicity overlapping in part with PD-like neurodegeneration, which is dealt with in Section 4.

4. Methamphetamine toxicity and autophagy: past controversies and novel insights

When administered chronically and/or at high doses, METH may produce toxicity in specific brain regions or even in peripheral organs, mostly those receiving dense sympathetic innervation (Albertson et al., 1999; Darke et al., 2008; Ferrucci et al., 2019; Matsumoto et al., 2014; Volkow et al., 2010a). Although METH neurotoxicity was initially considered to be relevant only for DA axon terminals, the occurrence of METH-induced toxicity has been documented at the level of neuronal cell bodies within the SNpc, and also the ventral tegmental area (VTA) (Ares-Santos et al., 2014; Biagioni et al., 2019; Fornai et al., 2003; Granado et al., 2010; Kitamura et al., 2007; Kitamura, 2009; Liu and Dluzen, 2006; Hirata and Cadet, 1997; Sonsalla et al., 1996; O'Dell et al., 1991; Wagner et al., 1980). To our experience, a certain amount of cell loss is detectable only when very high doses of METH are administered, which corresponds to a loss of nigrostriatal DA terminals ranging over 80 % (Biagioni et al., 2019; Fornai et al., 2003). This is in line with the original article by Ares-Santos et al. where cupric silver staining (modified according to Beltramino and de Olmos) was employed to assess neuronal loss (Ares-Santos et al., 2014).

The neurotoxic effects of high doses of METH in both experimental models and human abusers are due to abnormal, mostly DA-related, oxidative events, which are known to alter proteostasis while impairing both autophagy and the proteasome system (Fig. 5, Da Luz et al., 2015; Fornai et al., 2006; Limanaqi et al., 2018b, 2019; Moratalla et al., 2017). The neurotoxic effects of METH within DA terminals and cell bodies are consistent with an increased risk to develop neurodegeneration overlapping with PD, which is now quite well established in METH abusers (Callaghan et al., 2012; Morrow et al., 2011; Rumpf et al., 2017). In fact, in catecholamine-containing cells, and within SNpc neurons of mice, METH produces neuronal inclusions reminiscent of Lewy bodies (Castino et al., 2008; Ferrucci et al., 2017; Fornai et al., 2003, 2004, 2006; Lazzeri et al., 2007, 2006; Lin et al., 2012). These are also documented in catecholamine-containing brainstem neurons of human METH abusers (Quan et al., 2004). METH-induced inclusions appear as multilamellar whorls which further develop as cytoplasmic inclusions staining for ubiquitin, alpha-synuclein, parkin, UchL1, and HSP70 (Castino et al., 2008; Ferrucci et al., 2017; Fornai et al., 2006,

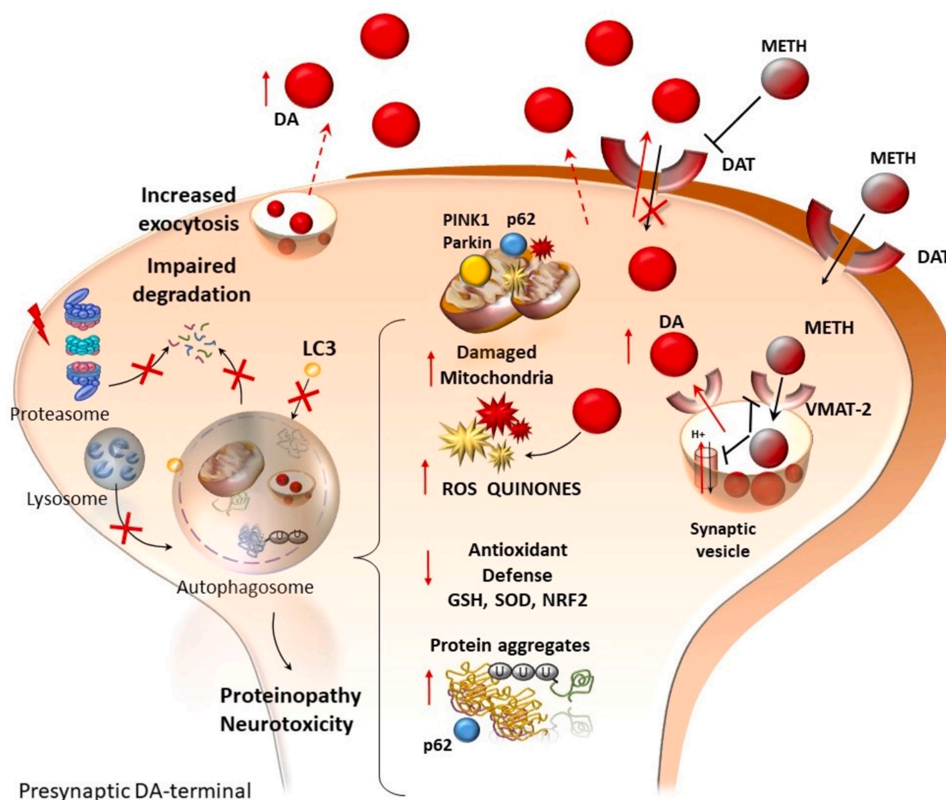


Fig. 5. METH-related effects of autophagy blockade within presynaptic DA terminals: from hyperdopaminergic state to protein aggregation and neurotoxicity. The neurotoxic effects of high doses of METH in both experimental models and human abusers are due to abnormal, mostly DA-related, oxidative events which are known to alter proteostasis while impairing both autophagy and the proteasome system. METH-induced alterations of DA metabolism generate toxic quinones and highly reactive chemical species that react with sulfhydryl groups to promote mitochondrial damage, along with structural modifications of lipids, nucleic acids, and proteins. Coupled with a decrease in the antioxidant defense systems, the burden of oxidized substrates and oxidative species contributes to impairing autophagy- and proteasome-mediated degradation. While altering behavior through a hyperdopaminergic state via enhanced DA release and decreased DA reuptake, this has deleterious effects at both synaptic terminals and cell bodies of DA neurons, driving p62-positive protein aggregation, cellular neuropathology, and cell death.

2003; Lazzeri et al., 2007, 2006; Lin et al., 2012). Most of these proteins are substrates of autophagy and the ubiquitin-proteasome system (UPS), which in fact, are both impaired in experimental models of METH and PD (Fig. 5, Fornai et al., 2006, 2003; Castino et al., 2008; Ferrucci et al., 2017; Lazzeri et al., 2006, 2007; Lin et al., 2012; Limanaqi et al., 2019, 2020a). In detail, in experimental models, pharmacological or genetic inhibition of either autophagy or the proteasome within DA neurons reproduces behavioral alterations and key pathological features of PD (Barroso-Chinea et al., 2015; Fornai et al., 2006; Lazzeri et al., 2006, 2007; Sato et al., 2018). The occurrence of multilamellar whorls, which is a witness of impaired autophagy, is similarly bound to lipid and cholesterol abnormalities in both PD and METH administration (Li et al., 2017; García-Sanz et al., 2018). In PD, this is related to mutations in the *GBA1* gene, which encodes an essential lysosomal enzyme called β-glucocerebrosidase (GCase) (García-Sanz et al., 2020). Similar to METH, which downregulates GCase, PD-related *GBA1* mutations cause GCase dysfunction fostering the accumulation of cholesterol and alpha-synuclein (Li et al., 2017; García-Sanz et al., 2020). This is associated with altered autophagosome trafficking and autophagy-lysosome function in both METH and PD models.

As mentioned above, the occurrence of neuronal inclusions and cell-clearance impairment, which similarly occurs in both METH and parkinsonism, is bound to alterations of DA metabolism via the generation of toxic quinones and highly reactive chemical species. These species react with sulfhydryl groups to promote structural modifications of lipids, nucleic acids, and proteins within DA axon terminals and surrounding compartments (Cadet et al., 1994; Cubells et al., 1994; Jayanthi et al., 1998; LaVoie and Hastings, 1999; Sulzer and Zecca, 1999; O'Dell et al., 1991; Gluck et al., 2001; Guillot et al., 2008; Lazzeri et al., 2007; Miyazaki et al., 2006). The burden of cytosolic catecholamine overwhelming vesicular storage, as it occurs during METH administration, may lead to catecholamine self-oxidation and subsequent formation of toxic by-products contributing to protein peroxidation and aggregation, along with mitochondrial and autophagy/UPS dysfunctions (Da Luz et al., 2015; Ferrucci et al., 2017; Jinsmaa et al., 2020; Kang et al., 2020). Reactive DA by-products are key to generating free radicals and producing mitochondrial damage, protein aggregation, and impairment of autophagy-lysosomal function. This occurs through either impaired fusion of autophagosomes with lysosomes, or engulfment of autophagy compartments by protein aggregates (Fig. 4, Muñoz et al., 2012; da Luz et al., 2015; He et al., 2018; Kang et al., 2020). Autophagy and the UPS represent the most powerful intracellular defense to counteract oxidative damage, which instead is generated by METH through inhibition of both clearing pathways. In fact, METH disassembles the proteasome and inhibits UPS activity, while UPS inhibitors produce subcellular alterations and neurotoxicity that overlap with those produced by METH (Barroso-Chinea et al., 2015; Fornai et al., 2006; Lazzeri et al., 2006; Limanaqi et al., 2019; Lin et al., 2012; Moszczynska and Yamamoto, 2011). On the other hand, autophagy is quickly recruited during METH in catecholamine-containing PC12 cells and rat DA cells (Cubells et al., 1994; Larsen et al., 2002; Lin et al., 2012) and *in vivo*, within catecholamine and striatal cells (Fornai et al., 2003; Lazzeri et al., 2007; Weinshenker et al., 2008). Being originally documented by Cubells et al. (Cubells et al., 1994), and further confirmed by Larsen et al. (Larsen et al., 2002), this was first suggested to produce autophagy-mediated cell damage. Increased levels of autophagy-related genes and proteins indicating abnormal autophagy recruitment have been documented in the brain of both METH-treated animals and human abusers (Khoshsirat et al., 2020; Lin et al., 2012; Subu et al., 2020; Xie et al., 2018). However, despite a massive engagement of autophagy, which should sort neuroprotection, autophagy inhibition *in vitro* was shown to exacerbate the effects of METH, which suggests that METH impairs autophagy instead (Castino et al., 2008; Lazzeri et al., 2018). This has been related to either the high amount of substrates (ROS, misfolded proteins, and damaged mitochondria) engulfing this clearing system (Castino et al., 2008; Da Luz et al., 2015; Lin et al., 2012; Xie et al., 2018) or to METH-induced collapse in vesicles acidification impairing fusion of autophagosomes with lysosomes (Tallóczy et al., 2008). Therefore, despite autophagy vacuoles and markers being over-expressed following METH administration/intake (Cubells et al., 1994; Larsen et al., 2002; Subu et al., 2020; Khoshsirat et al., 2020; Xie et al., 2018), autophagy activity may not be effective due to a lack of autophagy flux progression. Nonetheless, the largest amount of data on METH-induced autophagic changes are obtained mostly in cell culture systems, leaving unanswered the question of whether similar occurrences might be evident in human abusers or animal models that better mimic human MUD. In this frame, it is worth mentioning that differences in terms of METH-induced, cytopathologic and neurotoxic effects may be observed depending on the experimental conditions of METH treatment. Besides *in vitro* vs *in vivo* METH administration, METH dosage, and timing, these differences also concern the cellular models or animal species employed (mice *vs* rats), as well as experimenter- or self-administered METH paradigms (Gesi et al., 2001; Marshall and O'Dell, 2012; Subu et al., 2020). An increase in the expression and protein levels of both autophagy and apoptotic markers has been recently detected both in the prefrontal cortex of post-mortem METH users (Khoshsirat et al., 2020), as well as rodent models of experimenter-administered, and compulsive, self-administered METH paradigm (Xie et al., 2018; Subu et al., 2020). Intriguingly, within the striata of METH-treated rats, a marked overproduction of p62 occurs despite the over-expressions of BECN1 and LC3-II, which is a witness of deficient autophagy vesicle turnover and impaired autophagy flux (Xie et al., 2018). In line with this, enhancing autophagy via mTOR or GSK-β inhibition has been shown to protect against METH toxicity both *in vitro* and *in vivo* (Lazzeri et al., 2018; Li et al., 2017; Xie et al., 2018). Occasionally, evidence has been provided showing that autophagy inhibition may instead abolish METH-induced cell death, though most reports converge in that autophagy represents a compensatory defense mechanism in the early stress response induced by METH (Cao et al., 2016, 2017; Lin et al., 2012; Ma et al., 2014; Pitaksalee et al., 2015). Further *in vivo* studies employing autophagic modulators are needed to elucidate such an issue, which is currently under investigation in our Lab.

Autophagy recruitment as an early compensatory response to cope with protein overload, as it occurs following METH administration, may be bound to UPS inhibition (Kageyama et al., 2014; Li et al., 2019; Minoia et al., 2014). However, autophagy activation following UPS impairment appears to be only transient, as long-lasting UPS dysfunction impedes mitophagy and the recruitment of autophagosome markers (Ugun-Klusek et al., 2017). This fits with recent evidence showing that UPS activity, rather than inhibition, promotes autophagy by fostering both the nuclear translocation of TFEB and mTOR degradation, which eventually leads to mTOR downregulation and its detachment from the lysosomes (Follo et al., 2019).

METH-induced impairment of autophagy flux is evident by the dramatic increase in LC3 immunofluorescent puncta that have been interpreted as stagnant autophagy vacuoles (Castino et al., 2008). However, a recent study documented that METH administration, rather than a mere engulfment of autophagy compartments, produces a miss-compartmentalization of LC3 particles from autophagy vacuoles to the cytosol or non-canonical membranous compartments (Lazzeri et al., 2018). In fact, following METH administration, LC3 particles increase way more in the cytosol than within vacuoles, as measured through stochiometric count at transmission electron microscopy. While providing a novel insight into the mechanisms of action of METH on autophagy, this leads to reconsider the significance of the abundant, densely fluorescent LC3 spots that are detected at confocal microscopy; indeed, the greatest contribution is provided by LC3 that is stochastically distributed in cytosolic compartments other than autophagy vacuoles (Fig. 6, Lazzeri et al., 2018). In these same experimental conditions, the effects of the mTOR inhibitor and autophagy inducer rapamycin are demonstrated to be neuroprotective against cell death, meanwhile reinstating vacuolar compartmentalization of LC3. On the

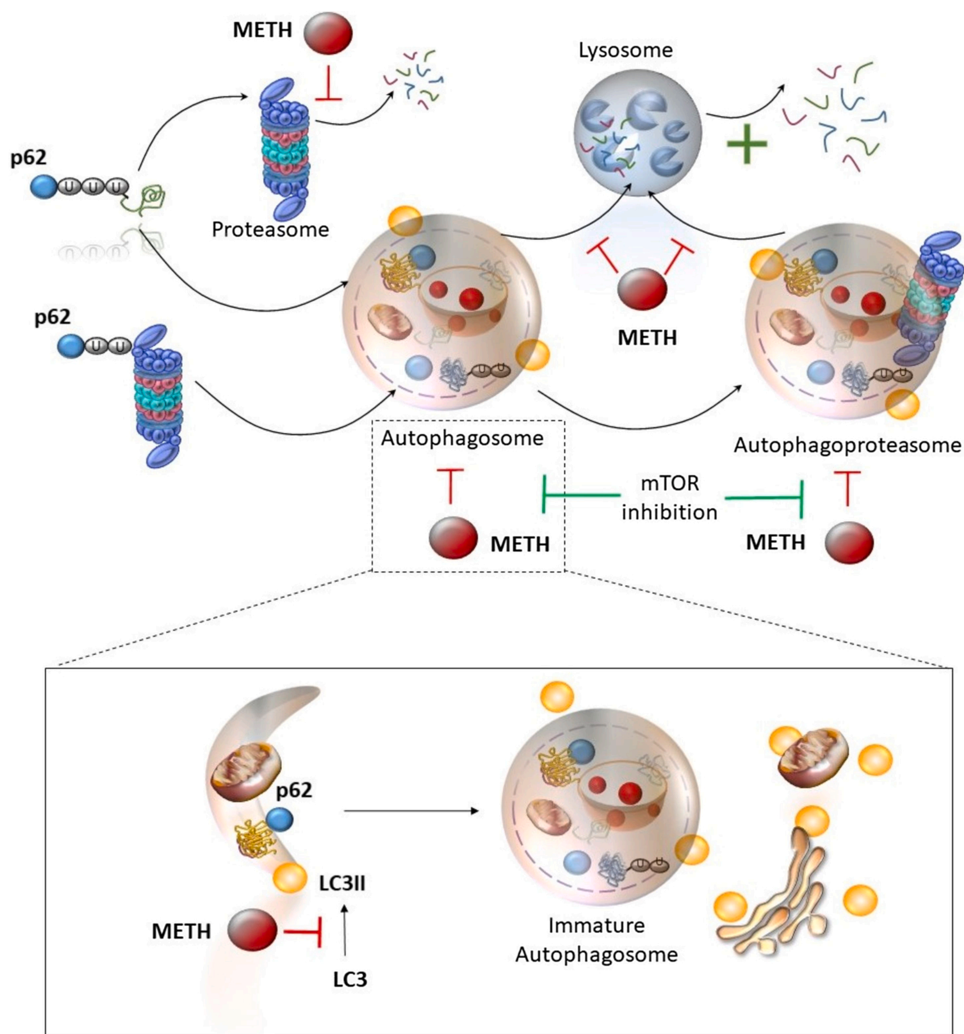


Fig. 6. METH impairs autophagy, the proteasome, and the "autophagoproteasome". METH impairs proteasomal degradation through oxidative-related proteasome damage and disassembly/inactivation of proteasome subunits. Ubiquitin- and p62-positive substrates, including the proteasome itself, are thus directed to autophagosomes merging with lysosomes, where cargo degradation is expected to take place. However, METH impairs autophagy-dependent protein degradation at several levels, and it also occludes the shuttling of proteasomes within autophagy compartments known as "autophagoproteasomes". METH-induced autophagy impairment may be due to engulfment of autophagy vacuoles by the burden of altered substrates, impaired autophagy flux due to vesicle alkalization, or METH-induced miscompartmentalization of LC3 particles (insert). In fact, METH displaces LC3 particles from autophagy vacuoles to the cytosol or non-canonical membranous compartments such as mitochondria and endoplasmic reticula, which suggests that METH-induced autophagy vacuoles correspond to immature autophagosomes.

other hand, co-administration of METH and asparagine, an mTOR inducer that also impairs the merge between autophagosomes and lysosomes, produces a dramatic effect on both LC3 compartmentalization and METH-induced cell damage. In such an experimental frame, the occurrence of autophagy vacuoles was further dissected for the concomitant presence of the P20S proteasome (Lazzeri et al., 2018). This was done in light of a recently described cell clearing organelle hosting both autophagy and proteasome components, which corresponds to the "autophagoproteasome" as being defined in "Guidelines for the Use and Interpretation of Assays for Monitoring Autophagy (3rd Edition)" (Klionsky et al., 2016). As described in the same guidelines, the convergence of proteasome within autophagy vacuoles has also been documented by Cohen-Kaplan et al. (2019), which is defined as "proteaphagy" to indicate autophagy-dependent degradation of inactive proteasomes. If this is the case, then one should expect a dramatic increase of autophagy vacuoles hosting proteasome subunits following METH administration, since METH disassembles and inactivates the proteasome. Instead, such a specific cell compartment (corresponding to LC3 + P20S-positive vacuole) is dramatically impaired by METH, while it is rescued by mTOR inhibition, which correlates with cell survival. When coupled with evidence that mTOR inhibition potentiates overall UPS activity besides autophagy (Zhao et al., 2015), this suggests that a concomitant acceleration of catalytic activity may concur to provide neuroprotection within such a unique cell compartment merging autophagy and proteasome systems (Fig. 6). The co-occurrence of alpha-synuclein and p62 within the autophagoproteasome, as documented by immunoprecipitation experiments, strengthens the potentially synergistic neuroprotective effect of autophagy-proteasome merging. This is liley to counteract both protein aggregation and impaired mitophagy that are triggered by METH. In fact, besides the well-known role of autophagy in the removal of damaged mitochondria, some key steps in mitochondrial removal are carried out by UPS components acting early during autophagosome formation (Lenzi et al., 2012; Song et al., 2016). This is in line with increasing evidence pinpointing the plethora of cross-talk mechanisms that occur between autophagy and the UPS (Limanaqi et al., 2020a).

In summary, since both UPS and autophagy blockers worsen METH toxicity, and in turn, METH impairs the merging of autophagy and proteasome (Castino et al., 2008; Fornai et al., 2006; Lazzeri et al., 2006, 2018; Limanaqi et al., 2019), a combined defect in both autophagy and proteasome likely paves the way to deleterious effects induced by DA-related oxidative species, which are abundantly produced by such a drug of abuse.

4.1. *Autophagy and METH toxicity beyond DA neurons*

Besides DA terminals/neurons, METH-induced neuronal inclusions, and even neurotoxicity may extend to postsynaptic GABA neuronal cell bodies throughout the striatum (Deng and Cadet, 2000; Jayanthi et al., 2005; Lazzeri et al., 2007; Tulloch et al., 2011; Zhu et al., 2006a, 2006b), making it reminiscent of specific striatal neurodegenerative disorders such as Huntington disease (HD). In this frame, key events which are

triggered by METH might all converge to accelerate neuronal cell loss within striatal neurons, encompassing the extracellular, paracrine diffusion of DA and DA-derived oxidative species, abnormal activation of D1DR and GLUT receptors, as well as GLUT-induced excitotoxicity (Jakel and Maragos, 2000; Wersinger et al., 2004). Remarkably, autophagy fosters GLUT receptor internalization and degradation, which is key to preventing both behavioral alterations, and Ca2+-related excitotoxicity that is related to abnormal GLUT receptor stimulation induced by METH (Fig. 4, Kulbe et al., 2014; Scheyer et al., 2016; Shehata et al., 2018, 2012). In fact, while sustaining drug addiction, enhanced GLUT release may produce Ca_{2+}-related excitotoxicity by promoting abnormal stimulation of AMPAR/NMDAR, which is coupled to enhanced PKC signaling pathway, and autophagy flux suppression (Battaglia et al., 2002a, b; Velásquez-Martinez et al., 2012; Kulbe et al., 2014). This is remarkable since enhanced PKC signaling is related to METH-induced neurotoxicity associated with both autophagy and UPS impairment (Huang et al., 2015; Lin et al., 2012). This configures PKC as a hub in the autophagy-related addictive and neurotoxic effects of METH.

Again, autophagy is seminal for the survival of norepinephrine (NE)-containing neurons of the A1/C1 cell group of the rostral ventrolateral medulla (RVLM) (Du et al., 2017), which are affected by METH to produce hypertension and cardiovascular collapse (Li et al., 2012). In detail, rescuing autophagy prevents excitotoxicity in the RVLM neurons, which produces a hypotensive effect with attenuated neuroinflammation compared with stress-induced hypertensive animals (Du et al., 2017). These autophagy-related effects are accompanied by reduced GLUT release and restoration of GABA levels. This is key since RVLM neurons are markedly affected by METH-induced cell death, which is associated with biochemical events that are related to autophagy dysfunctions (Lai et al., 2020; Li et al., 2012). These include mitochondrial failure, oxidative damage, and GLUT-related excitotoxicity through PKC hyper-activation (Lai et al., 2020; Li et al., 2012). These findings potentially extend the role of autophagy to the deleterious systemic effects of METH, which are bound to damage within sympathetic catecholamine neurons of the brainstem.

Although confirmatory studies are needed, one might speculate that autophagy impairment within NE neurons may occur following METH-induced accumulation of oxidative catecholamine by-products. In fact, in brain areas where NE terminals are more abundant compared with DA terminals, such as the hippocampus and prefrontal cortex, most of the extracellular DA is taken-up by the NET. However, when DA β hydroxylase (DβH) becomes saturated and rate-limiting, not all of the DA in the vesicle is converted to NA, which might provide a rationale for early oxidative-related alterations occurring within NE-containing neurons (Taylor et al., 2014). In fact, the burden of cytosolic catecholamine overwhelming vesicular storage may lead to both DA and NE self-oxidation and subsequent formation of toxic by-products contributing to neuroinflammation, protein peroxidation, and aggregation, up to organelles dysfunctions and autophagy impairment (Jinsmaa et al., 2020; Kang et al., 2020). This is key since the preservation of NA neurons plays a key role in neuroprotection against METH by modulating the sensitivity of striatal DA terminals (Fornai et al., 1995, 1998, 1999; Weinshenker et al., 2008). In fact, damage to NE-containing neurons, as obtained through the administration of N-(2-chloroethyl)-N-ethyl-2--bromobenzylamine (DSP-4) within the locus coeruleus (LC), exacerbates METH-induced damage to nigrostriatal DA terminals (Fornai et al., 1995, 1998, 1999; Weinshenker et al., 2008). Genetic deletion of DBH and acute treatment of wild-type mice with a DBH inhibitor (fusaric acid) recapitulates the effects of DSP-4 lesions on METH responses. Remarkably, cytoplasmic and nuclear whorls and autophagy-like structures are observed in striatal neurons after NA depletion, which is enhanced following METH treatment (Weinshenker et al., 2008). Coupled with evidence documenting that NE induces protective autophagy (Aránguiz-Urroz et al., 2011; Farah et al., 2014; Campos et al., 2020), a potential role of autophagy in the neuroprotective effects of NE against METH toxicity emerges, which deserves to be investigated.

5. Autophagy, neuroinflammation, and METH

METH-induced potentiation of DA release plays a key role in neuroinflammation by stimulating surrounding glial cells while triggering neurotoxic cascades (Ares-Santos et al., 2013, 2014; Granado et al., 2011; Moratalla et al., 2017; Thomas et al., 2008). GLUT-mediated mechanisms are also involved in the neuroinflammatory cascades accompanying progressive nigrostriatal degeneration in PD models (Ambrosi et al., 2010). Early activation and microglia and astrocytes rapidly occur after METH administration in DA-innervated areas, as shown by an increase in glial fibrillary acidic protein (GFAP) and microglial integrin-αM immunoreactivity in the striatum, hippocampus, and prefrontal cortex of METH-treated animals (Ares-Santos et al., 2013; Krasnova et al., 2010; LaVoie et al., 2004; Moratalla et al., 2017; Namyen et al., 2020; Tehrani et al., 2019; Thomas et al., 2008). Remarkably, impaired autophagy is correlated with increased neuroinflammation, augmented astrogliosis, apoptosis, and histological alterations occurring in the prefrontal cortex of METH-treated rats (Tehrani et al., 2019).

Within glial cells, METH activates nuclear factor-kappa B (NF-κB) to promote the transcription of pro-inflammatory cytokines and mediators, including the Nod-like Receptor Protein 3 (NLRP3) inflammasome (Du et al., 2019; Namyen et al., 2020; Shah et al., 2012; Snider et al., 2012). This leads to the release of various pro-inflammatory factors that perpetuate METH-induced neuroinflammation, such as interleukin 6 (IL-6), interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α), monocyte chemo-attractant protein 1 (MCP-1), matrix metalloproteinase-9 (MMP-9) enzyme, cellular adhesion molecule (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and NAD(P)H oxidase 2 (NOX2) (Du et al., 2019; Gonçalves et al., 2008; Namyen et al., 2020; Shah et al., 2012; Snider et al., 2012).

Microglial activation following METH exposure is also bound to the neuronal release of damage-associated molecular patterns (DAMPs). This is the case of high-mobility group box-1 (HMGB1), which is upregulated by METH in experimental animals and promotes neuroinflammatory responses in the VTA, nucleus accumbens, and prefrontal cortex (Frank et al., 2016). In basal conditions, HMGB1 promotes autophagy, while in the presence of high amounts of misfolded alpha-synuclein, as it occurs during METH administration, HMGB1 contributes to autophagy impairment (Song et al., 2014). Autophagy failure may in turn promote the extracellular release of DAMPs and pro-inflammatory factors. In fact, when a failure in the autophagy-lysosome pathway occurs, the extracellular release of indigested autophagy substrates represents an unconventional solution to avoid the intracellular accumulation of DAMPs, including oxidized/glycated/aggregated proteins, depolarized mitochondria leaking ROS, HMGB1, and NLRP3 inflammasome (Han et al., 2019; Rubinsztein et al., 2015; Zhang and Schekman, 2013). DAMPs are released extracellularly either as free compounds or via exosomes that derive from the fusion of autophagy-lysosome vacuoles with the plasma membrane. In neighboring cells, including neurons and glia, these DAMPs bind to toll-like receptors (TLRs) and AGE receptors (RAGEs), thus activating downstream oxidative and inflammatory signaling pathways which converge to impairing autophagy, such as nuclear factor (NF)-κB/NLRP3, PKC, PI3K/Akt/ mTOR (Lai et al., 2018; Limanaqi et al., 2020a; Pla et al., 2014; Song et al., 2014). In this way, indigested DAMPs may perpetuate oxidative and inflammatory damage meanwhile impinging on autophagy in the surrounding neuronal/glial milieu.

Remarkably, METH-induced microglial activation is bound to the formation of DA-quinones and subsequent activation of Toll-like receptor 4 (TLR4), as well as sigma-1 receptor-induced activation of the mitogen-activated protein kinase (MAPK) and PI3K/Akt pathways (Chao et al., 2017; Thomas et al., 2008). Besides the MAPK and PI3K/Akt pathways, which are both bound to autophagy inhibition, TLR4 stimulation also impairs autophagy and the UPS (Lai et al., 2018; Pla et al., 2014). For instance, NLRP3, which is implicated in

METH-induced microglial activation (Du et al., 2019), inhibits autophagy through TLR4 stimulation in microglial cells, which enhances the processing and release of mature IL-1β (Lai et al., 2018). Abnormal activation of the HMGB1/RAGE axis within NE-containing neurons of the RVLM impairs microglial autophagy and mitophagy, to promote neuroinflammation in mice models of stress (Zhang et al., 2020). Again, autophagy inhibition in microglia aggravates neurotoxin-induced neurodegeneration within DA neurons by promoting NLRP3 inflammasome activation (Qin et al., 2020). These findings indirectly suggest that METH-induced autophagy impairment may be implicated in the neuro-inflammatory events bridging the abnormal release of DA and DAMPs with microglial activation (Fig. 7).

METH-induced release of pro-inflammatory factors also promotes disruption of the blood-brain barrier (BBB), as documented by the loss of zonula occludens (ZO)-1, occludin, and claudin-5 tight junction proteins in rats (Namyen et al., 2020). Besides the upregulation of NF-κB-related pro-inflammatory genes and proteins, this is bound to the suppression of the anti-oxidative signaling factor Nrf2 (Namyen et al., 2020). Nrf2 deficiency potentiates METH-induced DA axonal damage, gliosis, and the release of pro-inflammatory cytokines in the mouse striatum (Granado et al., 2011). Remarkably, Nrf2 activation is known to bridge autophagy/mitophagy induction with reduction of oxidative stress, and inhibition of neuronal apoptosis. In fact, in the brain of mice featuring impaired autophagy due to Atg7 ablation, increased oxidative stress occurs, which promotes p53 activation and neurodegeneration (Yang et al., 2020a, b). When *Atg7* is deleted concomitantly with Nrf2, animals' death rapidly occurs, indicating an interdependency between autophagy, apoptotic, and Nrf2 stress response mechanisms (Yang et al., 2020a, b). Again, among a variety of ubiquitinated proteins, the adaptor protein p62 also binds to the Nrf2 inhibitor Keap1 (Ichimura et al., 2013; Taguchi et al., 2012). This leads to Keap1 degradation via autophagy, thus leaving Nrf2 free to accumulate and translocate in the nucleus where it promotes the transcription of antioxidant and detoxifying genes (Ichimura et al., 2013; Taguchi et al., 2012). In METH-treated animals, administration of melatonin, which has been shown to induce protective autophagy through SIRT-1 activation or mTOR inhibition (Boga et al., 2019), counteracts neuroinflammation and BBB leakage by rescuing Nrf2 (Namyen et al., 2020). Similar effects are produced by lithium, which attenuates METH-induced apoptosis, oxidative stress, and inflammation in the rat hippocampi (Mehrafza et al., 2019).

The involvement of autophagy in METH-induced disruption of the BBB has been confirmed *in vitro* in human brain microvascular endothelial cells (HBMECs) and human umbilical vein endothelial cells (HUVECs) (Ma et al., 2014). Within these cells, acute METH exposure induces autophagy as an early prosurvival response via inactivation of Akt/mTOR and upregulation of the ERK1/2 pathway. Remarkably, despite the inactivation of Akt/mTOR, and the increase in Beclin1 and LC3 recruitment, treatment with autophagy inhibitors accelerates METH-induced apoptosis instead of providing protection within brain endothelial cells (Ma et al., 2014). This confirms a beneficial effect for autophagy recruitment during METH-induced neuroinflammation and apoptosis.

6. Conclusions

In the present review, we discussed evidence suggesting that METH-induced alterations in neurotransmission and neurotoxicity may be bound to impaired autophagy and subsequent mishandling of neurotransmitter release and unfolded/misfolded proteins. Altered autophagy following METH exposure is likely to be due to the joined contribution of oxidative DA by-products and non-canonical biochemical cascades that are triggered by abnormal stimulation of post-synaptic DA and GLUT receptors. Recent insights provided into the mechanisms of action of METH suggest that such a drug of abuse may early affect the autophagy machinery by impairing the recruitment of key components that are required for autophagosome formation and maturation (Lazzeri et al., 2018). Considering the role of autophagy in the modulation of DA-related behavior, this appears as a key for METH-induced behavioral sensitization beyond neuroinflammation and neurotoxicity. It is fascinating that METH takes away the identity of specific synaptic compartments, by acting on both strictly degradative, autophagy-dependent mechanisms, and those involved in neurotransmitter release and

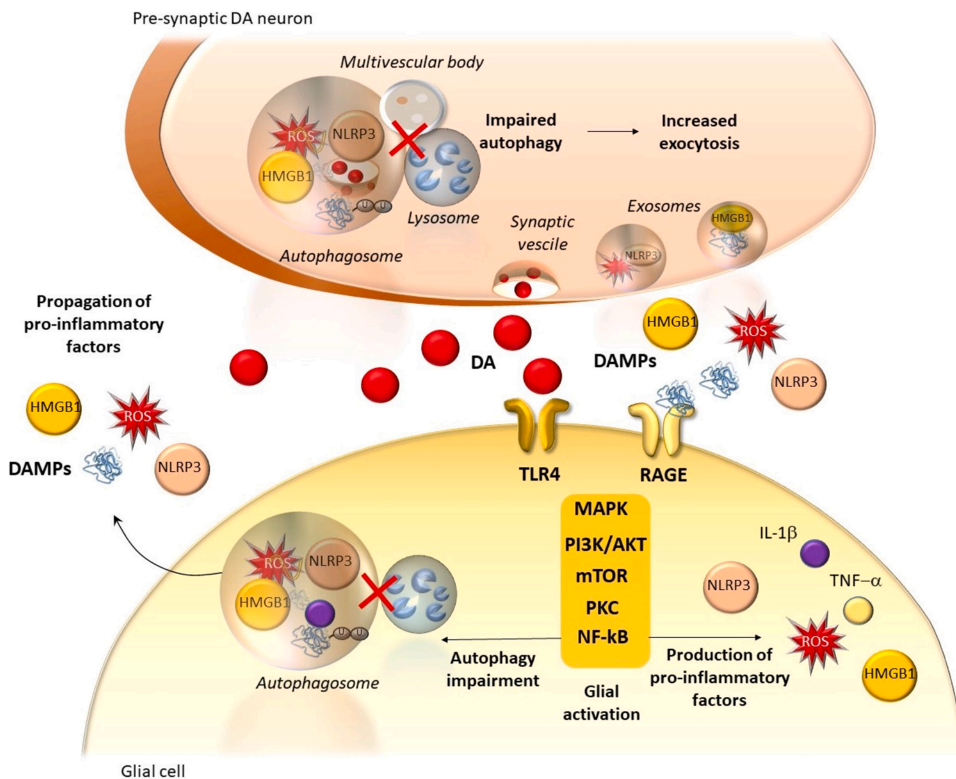


Fig. 7. Autophagy bridging DA-related and neuroinflammatory effects of METH. Within DA presynaptic terminals, autophagy impairment, which may include the impaired merging of autophagosomes and multivesicular bodies with lysosomes, leads to increased exocytosis promoting the extracellular release of both DA and substrates acting as danger-related molecular patterns (DAMPs). These include high-mobility group box-1 (HMGB1), NLRP3 inflammasome, Reactive Oxygen Species (ROS) and depolarized mitochondria leaking ROS, and altered protein substrates. Similar to DA, these promote glial activation through toll-like receptor 4 (TLR4) and receptors for advanced glycation end-products (RAGE). The binding of these receptors to DAMPs and DA is coupled to intracellular pathways such as mitogen-activated protein kinase (MAPK), mTOR, PKC, and nuclear factor (NF)-kB, which converge to promoting both the expression of pro-inflammatory factors and autophagy impairment. In turn, autophagy flux impairment contributes to the glial release of pro-inflammatory mediators acting as DAMPs, which perpetuates METH-induced inflammation in the surrounding milieu.

re-uptake crossing back again autophagy. The impressive overlap that emerges between the effects of METH and autophagy impairment upon DA system alterations, suggests that autophagy dysfunction may bridge drugs of abuse, psychiatric signs, and neurodegeneration. In fact, autophagy alterations following METH intake/administration are intermingled with a chain of events starting from synaptic insults up to neuronal damage, which could predispose to maladaptive behavioral changes and neurodegenerative phenomena. This is key since psychiatric symptoms and signs are often overrepresented and may even precede the onset of neurodegeneration. Joined with evidence that autophagy dysfunctions occur in both mental disorders, and early on, during neurodegeneration, we propose that autophagy may serve as a gateway to understanding the psychiatric manifestations and neurodegenerative phenomena associated with MUD-related addiction and neurotoxicity.

Author contributions

Conceptualization: Francesco Fornai; Writing - original draft, review & editing: Francesco Fornai and Fiona Limanaqi; Writing -review & editing: Fiona Limanaqi, Carla L. Busceti, Roberta Celli, Francesca Biagioni; Art-work: Fiona Limanaqi; Supervision Francesco Fornai.

Funding

This work is funded by Ministero della Salute (Ricerca Corrente 2021) and University of Pisa (Funds from Dept. of Translational Research and New Technologies in Medicine and Surgery).

Declaration of Competing Interest

The authors have no competing interests to declare.

Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and Supplementary data associated with this article can be found in the online version, at doi:https://doi.org/10.1016/j.pneurobio.2021.102112.

References

Abi-dargham, A., Moore, H., 2003. Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. Neuroscientist 9, 404–416. https://doi.org/10.1177/1073858403252674.

Agid, Y., Javoy, F., Youdim, M.B., 1973. Monoamine oxidase and aldehyde dehydrogenase activity in the striatum of rats after 6-hydroxydopamine lesion of the nigrostriatal pathway. Br. J. Pharmacol. 48, 175–178. https://doi.org/10.1111/j.1476-5381.1973.tb08238.x.

Ago, Y., Tanaka, T., Kita, Y., Tokumoto, H., Takuma, K., Matsuda, T., 2012. Lithium attenuates methamphetamine-induced hyperlocomotion and behavioral sensitization via modulation of prefrontal monoamine release. Neuropharmacology 62, 1634–1639. https://doi.org/10.1016/j.neuropharm.2011.10.004.

Albertson, T.E., Derlet, R.W., Van Hoozen, B.E., 1999. Methamphetamine and the expanding complications of amphetamines. West. J. Med. 170, 214–219.

Ali, T., Rahman, S.U., Hao, Q., Li, W., Liu, Z., Ali Shah, F., Murtaza, I., Zhang, Z., Yang, X., Liu, G., Li, S., 2020. Melatonin prevents neuroinflammation and relieves depression by attenuating autophagy impairment through FOXO3a regulation. J. Pineal Res. 69, e12667 https://doi.org/10.1111/jpi.12667.

Ambrosi, G., Armentero, M.T., Levandis, G., Bramanti, P., Nappi, G., Blandini, F., 2010. Effects of early and delayed treatment with an mGluR5 antagonist on motor impairment, nigrostriatal damage and neuroinflammation in a rodent model of Parkinson's disease. Brain Res. Bull. 82, 29–38. https://doi.org/10.1016/j.brainresbull.2010.01.011.

Aránguiz-Urroz, P., Canales, J., Copaja, M., Troncoso, R., Vicencio, J.M., Carrillo, C., Lara, H., Lavandero, S., Díaz-Araya, G., 2011. Beta(2)-adrenergic receptor regulates cardiac fibroblast autophagy and collagen degradation. Biochim. Biophys. Acta 1812, 23–31. https://doi.org/10.1016/j.bbadis.2010.07.00.

Ares-Santos, S., Granado, N., Moratalla, R., 2013. The role of dopamine receptors in the neurotoxicity of methamphetamine. J. Intern. Med. 273, 437–453. https://doi.org/10.1111/joim.12049.

Ares-Santos, S., Granado, N., Espadas, I., Martinez-Murillo, R., Moratalla, R., 2014. Methamphetamine causes degeneration of dopamine cell bodies and terminals of the nigrostriatal pathway evidenced by silver staining. Neuropsychopharmacology 39, 1066–1080. https://doi.org/10.1038/npp.2013.307.

Atkin, T.A., Brandon, N.J., Kittler, J.T., 2012. Disrupted in schizophrenia 1 forms pathological aggresomes that disrupt its function in intracellular transport. Hum. Mol. Genet. 21, 2017–2028. https://doi.org/10.1093/hmg/dds018.

Bachmann, R.F., Wang, Y., Yuan, P., Zhou, R., Li, X., Alesci, S., Du, J., Manji, H.K., 2009. Common effects of lithium and valproate on mitochondrial functions: protection against methamphetamine-induced mitochondrial damage. Int. J. Neuropsychopharmacol. 12, 805. https://doi.org/10.1017/S1461145708009802.

Bader, C.A., Shandala, T., Ng, Y.S., Johnson, I.R.D., Brooks, D.A., 2015. Atg9 is required for intraluminal vesicles in amphisomes and autolysosomes. Biol. Open 4, 1345–1355. https://doi.org/10.1242/bio.013979.

Barak, S., Liu, F., Hamida, S.Ben, Yowell, Q.V., Neasta, J., Kharazia, V., Janak, P.H., Ron, D., 2013. Disruption of alcohol-related memories by mTORC1 inhibition prevents relapse. Nat. Neurosci. 16, 1111–1117. https://doi.org/10.1038/nn.3439.

Barroso-Chinea, P., Thiolat, M.L., Bido, S., Martinez, A., Doudnikoff, E., Baufreton, J., Bourdenx, M., Bloch, B., Bezard, E., Martin-Negrier, M.L., 2015. D1 dopamine receptor stimulation impairs striatal proteasome activity in Parkinsonism through 26S proteasome disassembly. Neurobiol. Dis. 78, 77–87. https://doi.org/10.1016/j.nbd.2015.02.024.

Barroso-Chinea, P., Luis-Ravelo, D., Fumagallo-Reading, F., Castro-Hernandez, J., Salas-Hernandez, J., Rodriguez-Nuñez, J., Febles-Casquero, A., Cruz-Muros, I., Afonso-Oramas, D., Abreu-Gonzalez, P., Moratalla, R., Millan, M.J., Gonzalez-Hernandez, T., 2020. DRD3 (dopamine receptor D3) but not DRD2 activates autophagy through MTORC1 inhibition preserving protein synthesis. Autophagy 16, 1279–1295. https://doi.org/10.1080/15548627.2019.1668606.

Battaglia, G., Fornai, F., Busceti, C.L., Aloisi, G., Cerrito, F., De Blasi, A., Melchiorri, D., Nicoletti, F., 2002a. Selective blockade of mGlu5 metabotropic glutamate receptors is protective against methamphetamine neurotoxicity. J. Neurosci. 22, 2135–2141. https://doi.org/10.1523/JNEUROSCI.22-06-02135.2002.

Battaglia, G., Gesi, M., Lenzi, P., Busceti, C.L., Soldani, P., Orzi, F., Rampello, L., Nicoletti, F., Ruggieri, S., Fornai, F., 2002b. Morphological and Biochemical Evidence that Apomorphine Rescues Striatal Dopamine Terminals and Prevents Methamphetamine Toxicity. Ann. N. Y. Acad. Sci. 965, 254–266. https://doi.org/10.1111/j.1749-6632.2002.tb04167.x.

Beaulieu, J.M., Sotnikova, T.D., Yao, W.D., Kockeritz, L., Woodgett, J.R., Gainetdinov, R. R., Caron, M.G., 2004. Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. Proc. Natl. Acad. Sci. U. S. A. 101, 5099–5104. https://doi.org/10.1073/pnas.0307921101.

Beaulieu, J.M., Gainetdinov, R.R., Caron, M.G., 2009. Akt/GSK3 signaling in the action of psychotropic drugs. Annu. Rev. Pharmacol. Toxicol. 49, 327–347. https://doi.org/10.1146/annurev.pharmtox.011008.145634.

Beckley, J.T., Laguesse, S., Phamluong, K., Morisot, N., Wegner, S.A., Ron, D., 2016. The first alcohol drink triggers mTORC1-dependent synaptic plasticity in nucleus accumbens dopamine D1 receptor neurons. J. Neurosci. 36, 701–713. https://doi.org/10.1523/JNEUROSCI.2254-15.2016.

Beirami, E., Oryan, S., Seyedhosseini Tamijani, S.M., Ahmadiani, A., Dargahi, L., 2018. Intranasal insulin treatment restores cognitive deficits and insulin signaling impairment induced by repeated methamphetamine exposure. J. Cell. Biochem. 119, 2345–2355. https://doi.org/10.1002/jcb.26398.

Benavides, D.R., Bibb, J.A., 2004. Role of Cdk5 in drug abuse and plasticity. Ann. N. Y. Acad. Sci. 1025, 335–344. https://doi.org/10.1196/annals.1316.041.

Biagioni, F., Ferese, R., Limanaqi, F., Madonna, M., Lenzi, P., Gambardella, S., Fornai, F., 2019. Methamphetamine persistently increases alpha-synuclein and suppresses gene promoter methylation within striatal neurons. Brain Res. 1719, 157–175. https://doi.org/10.1016/j.brainres.2019.05.035.

Binotti, B., Pavlos, N.J., Riedel, D., Wenzel, D., Vorbrüggen, G., Schalk, A.M., Kühnel, K., Boyken, J., Erck, C., Martens, H., Chua, J.J.E., Jahn, R., 2014. The GTPase RaB26 links synaptic vesicles to the autophagy pathway. Elife 2015, 1–23. https://doi.org/10.7554/eLife.05597.001.

Binotti, B., Jahn, R., Chua, J., 2016. Functions of rab proteins at presynaptic sites. Cells 5, 7. https://doi.org/10.3390/cells5010007.

Birdsall, V., Waites, C.L., 2019. Autophagy at the synapse. Neurosci. Lett. 697, 24–28. https://doi.org/10.1016/j.neulet.2018.05.033.

Boga, J.A., Caballero, B., Potes, Y., Perez-Martinez, Z., Reiter, R.J., Vega-Naredo, I., Coto-Montes, A., 2019. Therapeutic potential of melatonin related to its role as an autophagy regulator: a review. J. Pineal Res. 66, e12534 https://doi.org/10.1111/jpi.12534.

Bosch, P.J., Benton, M.C., Macartney-Coxson, D., Kivell, B.M., 2015. mRNA and microRNA analysis reveals modulation of biochemical pathways related to addiction in the ventral tegmental area of methamphetamine self-administering rats. BMC Neurosci. 16, 43. https://doi.org/10.1186/s12868-015-0186-y.

Brandon, N.J., Sawa, A., 2011. Linking neurodevelopmental and synaptic theories of mental illness through DISC1. Nat. Rev. Neurosci. 12, 707–722. https://doi.org/10.1038/nrn3120.

Brodin, L., Shupliakov, O., 2018. Retromer in synaptic function and pathology. Front. Synaptic Neurosci. 10, 37. https://doi.org/10.3389/fnsyn.2018.00037.

Brown, J.M., Hanson, G.R., Fleckenstein, A.E., 2000. Methamphetamine rapidly decreases vesicular dopamine uptake. J. Neurochem. 74, 2221–2223. https://doi.org/10.1046/j.1471-4159.2000.0742221.x.

Brown, J.M., Quinton, M.S., Yamamoto, B.K., 2005. Methamphetamine-induced inhibition of mitochondrial complex II: roles of glutamate and peroxynitrite. J. Neurochem. 95, 429–436. https://doi.org/10.1111/j.1471-4159.2005.03379.x.

Brown, J.W.L., Dunne, J.W., Fatovic, D.M., Lee, J., Lawn, N.D., 2011. Amphetamine-associated seizures: clinical features and prognosis. Epilepsia 52, 401–404. https://doi.org/10.1111/j.1528-1167.2010.02924.x.

Cadet, J.L., Bisagno, V., 2016. Neuropsychological consequences of chronic drug use: relevance to treatment approaches. Front. Psychiatry 6, 189. https://doi.org/10.3389/fpsyt.2015.00189.

Cadet, J.L., Ali, S., Epstein, C., 1994. Involvement of oxygen-based radicals in methamphetamine-induced neurotoxicity: evidence from the use of CuZnSOD transgenic mice. Ann. N. Y. Acad. Sci. 738, 388–391. https://doi.org/10.1111/j.1749-6632.1994.tb21827.x.

Cadet, J.L., Jayanthi, S., McCoy, T.M., Beauvais, G., Sheng Cai, N., 2012. Dopamine D1 receptors, regulation of gene expression in the brain, and neurodegeneration. CNS Neurol. Disord. - Drug Targets 9, 526–538. https://doi.org/10.2174/187152710793361496.

Callaghan, R.C., Cunningham, J.K., Sykes, J., Kish, S.J., 2012. Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs. Drug Alcohol Depend. 120, 35–40. https://doi.org/10.1016/j.drugalcdep.2011.06.013.

Campos, J.C., Baehr, L.M., Ferreira, N.D., Bozi, L., Andres, A.M., Ribeiro, M., Gottlieb, R.A., Bodine, S.C., Ferreira, J., 2020. β2 -adrenoceptor activation improves skeletal muscle autophagy in neurogenic myopathy. FASEB J. 34, 5628–5641. https://doi.org/10.1096/fj.201902305R.

Cantrup, R., Sathanantham, K., Rushlow, W.J., Rajakumar, N., 2012. Chronic hyperdopaminergic activity of schizophrenia is associated with increased ΔFosB levels and cdk-5 signaling in the nucleus accumbens. Neuroscience 222, 124–135. https://doi.org/10.1016/j.neuroscience.2012.07.027.

Cao, L., Fu, M., Kumar, S., Kumar, A., 2016. Methamphetamine potentiates HIV-1 gp120-mediated autophagy via beclin-1 and Atg5/7 as a pro-survival response in astrocytes. Cell Death Dis. 7, e2425. https://doi.org/10.1038/cddis.2016.317.

Cao, L., Glazyrin, A., Kumar, S., Kumar, A., 2017. Role of autophagy in HIV pathogenesis and drug abuse. Mol. Neurobiol. 54, 5855–5867. https://doi.org/10.1007/s12035-016-0118-6.

Castino, R., Lazzeri, G., Lenzi, P., Bellio, N., Follo, C., Ferrucci, M., Fornai, F., Isidoro, C., 2008. Suppression of autophagy precipitates neuronal cell death following low doses of methamphetamine. J. Neurochem. 106, 1426–1439. https://doi.org/10.1111/j.1471-4159.2008.05488.x.

Cataldi, S., Follett, J., Fox, J.D., Tatarnikov, I., Kadgien, C., Gustavsson, E.K., Khinda, J., Milnerwood, A.J., Farrer, M.J., 2018. Altered dopamine release and monoamine transporters in Vps35 p.D620N knock-in mice. NPJ Park. Dis. 4, 27. https://doi.org/10.1038/s41531-018-0063-3.

Centonze, D., Picconi, B., Baunez, C., Borrelli, E., Pisani, A., Bernardi, G., Calabresi, P., 2002. Cocaine and amphetamine depress striatal GABAergic synaptic transmission through D2 dopamine receptors. Neuropsychopharmacology 26, 164–175. https://doi.org/10.1016/S0893-133X(01)00299-8.

Centonze, D., Grande, C., Saulle, E., Martin, A.B., Gubellini, P., Pavón, N., Pisani, A., Bernardi, G., Moratalla, R., Calabresi, P., 2003. Distinct roles of D1 and D5 dopamine receptors in motor activity and striatal synaptic plasticity. J. Neurosci. Sep 23, 8506–8512. https://doi.org/10.1523/JNEUROSCI.23-24-08506.2003.

Chang, W.H., Chen, K.C., Tseng, H.H., Chiu, N.T., Lee, I.H., Chen, P.S., Yang, Y.K., 2020. Bridging the associations between dopamine, brain volumetric variation and IQ in drug-naïve schizophrenia. Schizophr. Res. 220, 248–253. https://doi.org/10.1016/j.schres.2020.03.005.

Chao, J., Zhang, Y., Du, L., Zhou, R., Wu, X., Shen, K., Yao, H., 2017. Molecular mechanisms underlying the involvement of the sigma-1 receptor in methamphetamine-mediated microglial polarization. Sci. Rep. 7, 11540. https://doi.org/10.1038/s41598-017-11065-8.

Choi, J.K., Lim, G., Chen, Y.I., Jenkins, B.G., 2018. Abstinence to chronic methamphetamine switches connectivity between striatal, hippocampal and sensorimotor regions and increases cerebral blood volume response. Neuroimage 174, 364–379. https://doi.org/10.1016/j.neuroimage.2018.02.059.

Cleary, C., Linde, J.A.S., Hiscock, K.M., Hadas, I., Belmaker, R.H., Agam, G., Flaisher-Grinberg, S., Einat, H., 2008. Antidepressive-like effects of rapamycin in animal models: implications for mTOR inhibition as a new target for treatment of affective disorders. Brain Res. Bull. 76, 469–473. https://doi.org/10.1016/j.brainresbull.2008.03.005.

Cohen-Kaplan, V., Livneh, I., Kwon, Y.T., Ciechanover, A., 2019. Monitoring stress-induced autophagic engulfment and degradation of the 26S proteasome in mammalian cells. In: Methods in Enzymology, vol. 619. Academic Press Inc, pp. 337–366. https://doi.org/10.1016/bs.mie.2018.12.022.

Cruickshank, C.C., Dyer, K.R., 2009. A review of the clinical pharmacology of methamphetamine. Addiction 104, 1085–1099. https://doi.org/10.1111/j.1360-0443.2009.02564.x.

Cubells, J.F., Rayport, S., Rajendran, G., Sulzer, D., 1994. Methamphetamine neurotoxicity involves vacuolation of endocytic organelles and dopamine-dependent intracellular oxidative stress. J. Neurosci. 14, 2260–2271. https://doi.org/10.1523/jneurosci.14-04-02260.1994.

Cuervo, A.M., Wong, E., 2014. Chaperone-mediated autophagy: roles in disease and aging. Cell Res. 24, 92–104. https://doi.org/10.1038/cr.2013.153.

Da Luz, M.H.M., Peres, I.T., Santos, T.G., Martins, V.R., Icimoto, M.Y., Lee, K., 2015. Dopamine induces the accumulation of insoluble prion protein and affects autophagic flux. Front. Cell. Neurosci. 9, 12. https://doi.org/10.3389/fncel.2015.00012.

Dahoun, T., Trossbach, S.V., Brandon, N.J., Korth, C., Howes, O.D., 2017. The impact of Disrupted-in-Schizophrenia 1 (DISC1) on the dopaminergic system: a systematic review. Transl. Psychiatry 7, e1015. https://doi.org/10.1038/tp.2016.282.

Darke, S., Kaye, S., McKetin, R., Duflou, J., 2008. Major physical and psychological harms of methamphetamine use. Drug Alcohol Rev. 27, 253–262. https://doi.org/10.1080/09595230801923702.

Dayas, C.V., Smith, D.W., Dunkley, P.R., 2012. An emerging role for the mammalian target of rapamycin in "pathological" protein translation: relevance to cocaine addiction. Front. Pharmacol. 3, 13. https://doi.org/10.3389/fphar.2012.00013.

De Risi, M., Torromino, G., Tufano, M., Moriceau, S., Pignataro, A., Rivagorda, M., Carrano, N., Middei, S., Settembre, C., Ammassari-Teule, M., Gardoni, F., Mele, A., Oury, F., De Leonibus, E., 2020. Mechanisms by which autophagy regulates memory capacity in ageing. Aging Cell 19, e13189. https://doi.org/10.1111/acel.13189.

Dean, A.C., Groman, S.M., Morales, A.M., London, E.D., 2013. An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. Neuropsychopharmacology 38, 259–274. https://doi.org/10.1038/npp.2012.179.

Decressac, M., Mattsson, B., Weikop, P., Lundblad, M., Jakobsson, J., Björklund, A., 2013. TFEB-mediated autophagy rescues midbrain dopamine neurons from α-synuclein toxicity. Proc. Natl. Acad. Sci. U. S. A. 110, E1817. https://doi.org/10.1073/pnas.1305623110.

Deng, X., Cadet, J.L., 2000. Methamphetamine-induced apoptosis is attenuated in the striata of copper-zinc superoxide dismutase transgenic mice. Mol. Brain Res. 83, 121–124. https://doi.org/10.1016/S0169-328X(00)00169-8.

Dolma, S., Selvadurai, H.J., Lan, X., Lee, L., Kushida, M., Voisin, V., Whetstone, H., So, M., Aviv, T., Park, N., Zhu, X., Xu, C.J., Head, R., Rowland, K.J., Bernstein, M., Clarke, I.D., Bader, G., Harrington, L., Brumell, J.H., Tyers, M., Dirks, P.B., 2016. Inhibition of dopamine receptor D4 impedes autophagic flux, proliferation, and survival of glioblastoma stem cells. Cancer Cell 29, 859–873. https://doi.org/10.1016/j.ccell.2016.05.002.

Du, D., Hu, L., Wu, J., Wu, Q., Cheng, W., Guo, Yuhong, Guan, R., Wang, Y., Chen, X., Yan, X., Zhu, D., Wang, J., Zhang, S., Guo, Yanfang, Xia, C., 2017. Neuroinflammation contributes to autophagy flux blockage in the neurons of rostral ventrolateral medulla in stress-induced hypertension rats. J. Neuroinflammation 14, 169. https://doi.org/10.1186/s12974-017-0942-2.

Du, L., Shen, K., Bai, Y., Chao, J., Hu, G., Zhang, Y., Yao, H., 2019. Involvement of NLRP3 inflammasome in methamphetamine-induced microglial activation through miR-143/PUMA axis. Toxicol. Lett. 301, 53–63. https://doi.org/10.1016/j.toxlet.2018.10.020.

Erickson, J.D., Schäfer, M.K.H., Bonner, T.I., Eiden, L.E., Weihe, E., 1996. Distinct pharmacological properties and distribution in neurons and endocrine cells of two isoforms of the human vesicular monoamine transporter. Proc. Natl. Acad. Sci. U.S. A. 93, 5166–5171. https://doi.org/10.1073/pnas.93.10.5166.

Fader, C.M., Colombo, M.I., 2009. Autophagy and multivesicular bodies: two closely related partners. Cell Death Differ. 16, 70–78. https://doi.org/10.1038/cdd.2008.168.

Fang, E.F., Hou, Y., Palikaras, K., Adriaanse, B.A., Kerr, J.S., Yang, B., Lautrup, S., Hasan-Olive, M.M., Caponio, D., Dan, X., Rocktäschel, P., Croteau, D.L., Akbari, M., Greig, N.H., Fladby, T., Nilsen, H., Cader, M.Z., Mattson, M.P., Tavernarakis, N., Bohr, V.A., 2019. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat. Neurosci. 22, 401–412. https://doi.org/10.1038/s41593-018-0332-9.

Farah, B.L., Sinha, R.A., Wu, Y., Singh, B.K., Zhou, J., Bay, B.H., Yen, P.M., 2014. β-Adrenergic agonist and antagonist regulation of autophagy in HepG2 cells, primary mouse hepatocytes, and mouse liver. PLoS One 9, e98155. https://doi.org/10.1371/journal.pone.0098155.

Feier, G., Valvassori, S.S., Varela, R.B., Resende, W.R., Bavaresco, D.V., Morais, M.O., Scaini, G., Andersen, M.L., Streck, E.L., Quevedo, J., 2013. Lithium and valproate modulate energy metabolism in an animal model of mania induced by methamphetamine. Pharmacol. Biochem. Behav. 103, 589–596. https://doi.org/10.1016/j.pbb.2012.09.010.

Feng, Q., Luo, Y., Zhang, X.N., Yang, X.F., Hong, X.Y., Sun, D.S., Li, X.C., Hu, Y., Li, X.G., Zhang, J.F., Li, X., Yang, Y., Wang, Q., Liu, G.P., Wang, J.Z., 2020. MAPT/Tau accumulation represses autophagy flux by disrupting IST1-regulated ESCRT-III complex formation: a vicious cycle in Alzheimer neurodegeneration. Autophagy 16, 641–658. https://doi.org/10.1080/15548627.2019.1633862.

Ferese, R., Lenzi, P., Fulceri, F., Biagioni, F., Fabrizi, C., Gambardella, S., Familiari, P., Frati, A., Limanaqi, F., Fornai, F., 2020. Quantitative ultrastructural morphometry and gene expression of mTOR-Related mitochondriogenesis within glioblastoma cells. Int. J. Mol. Sci. 21, 1–35. https://doi.org/10.3390/ijms21134570.

Ferreras, S., Fernández, G., Danelon, V., Pisano, M.V., Masseroni, L., Chapleau, C.A., Krapacher, F.A., Mlewski, E.C., Mascó, D.H., Arias, C., Pozzo-Miller, L., Paglini, M. G., 2017. Cdk5 is essential for amphetamine to increase dendritic spine density in hippocampal pyramidal neurons. Front. Cell. Neurosci. 11, 372. https://doi.org/10.3389/fncel.2017.00372.

Ferrucci, M., Ryskalin, L., Biagioni, F., Gambardella, S., Busceti, C.L., Falleni, A., Lazzeri, G., Fornai, F., 2017. Methamphetamine increases prion protein and induces dopamine-dependent expression of protease resistant PrPsc. Arch. Ital. Biol. 155, 81–97. https://doi.org/10.12871/000398292017129.

Ferrucci, M., Limanaqi, F., Ryskalin, L., Biagioni, F., Busceti, C.L., Fornai, F., 2019. The effects of amphetamine and methamphetamine on the release of norepinephrine, dopamine and acetylcholine from the brainstem reticular formation. Front. Neuroanat. 13, 48. https://doi.org/10.3389/fnana.2019.00048.

Fiorentini, C., Busi, C., Gorruso, E., Gotti, C., Spano, P., Missale, C., 2008. Reciprocal regulation of dopamine D1 and D3 receptor function and trafficking by heterodimerization. Mol. Pharmacol. 74, 59–69. https://doi.org/10.1124/mol.107.043885.

Fleckenstein, A.E., Volz, T.J., Riddle, E.L., Gibb, J.W., Hanson, G.R., 2007. New insights into the mechanism of action of amphetamines. Annu. Rev. Pharmacol. Toxicol. 47, 681–698. https://doi.org/10.1146/annurev.pharmtox.47.120505.105140.

Floor, E., Meng, L., 1996. Amphetamine releases dopamine from synaptic vesicles by dual mechanisms. Neurosci. Lett. 215, 53–56. https://doi.org/10.1016/S0304-3940(96)12963-3.

Follo, C., Vidoni, C., Morani, F., Ferraresi, A., Seca, C., Isidoro, C., 2019. Amino acid response by Halofuginone in Cancer cells triggers autophagy through proteasome degradation of mTOR. Cell Commun. Signal 17, 39. https://doi.org/10.1186/s12964-019-0354-2.

Fornai, F., Bassi, L., Torracca, M.T., Scalori, V., Corsini, G.U., 1995. Norepinephrine loss exacerbates methamphetamine-induced striatal dopamine depletion in mice. Eur. J. Pharmacol. 283, 99–102. https://doi.org/10.1016/0014-2999(95)00313-A.

Fornai, F., Alessandrì, M.G., Torracca, M.T., Bassi, L., Scalori, V., Corsini, G.U., 1998. Noradrenergic modulation of methamphetamine-induced striatal dopamine depletion, in: annals of the New York Academy of Sciences. Blackwell Publishing Inc. 166–177. https://doi.org/10.1111/j.1749-6632.1998.tb08231.x.

Fornai, F., Giorgi, F.S., Alessandrí, M.G., Giusiani, M., Corsini, G.U., 1999. Effects of pretreatment with N-(2-chloroethyl)-N-ethyl-2- bromobenzylamine (DSP-4) on methamphetamine pharmacokinetics and striatal dopamine losses. J. Neurochem. 72, 777–784. https://doi.org/10.1046/j.1471-4159.1999.0720777.x.

Fornai, F., Lenzi, P., Gesi, M., Soldani, P., Ferrucci, M., Lazzeri, G., Capobianco, L., Battaglia, G., De Blasi, A., Nicoletti, F., Paparelli, A., 2003. Methamphetamine produces neuronal inclusions in the nigrostriatal system and in PC12 cells. J. Neurochem. 88, 114–123. https://doi.org/10.1046/j.1471-4159.2003.02137.x.

Fornai, F., Lenzi, P., Gesi, M., Ferrucci, M., Lazzeri, G., Capobianco, L., de Blasi, A., Battaglia, G., Nicoletti, F., Ruggieri, S., Paparelli, A., 2004. Similarities between methamphetamine toxicity and proteasome inhibition. Ann. N. Y. Acad. Sci. 1025, 162–170. https://doi.org/10.1196/annals.1316.021.

Fornai, F., Lazzeri, G., Bandettini Di Poggio, A., Soldani, P., De Blasi, A., Nicoletti, F., Ruggieri, S., Paparelli, A., 2006. Convergent roles of α-synuclein, DA metabolism, and the ubiquitin-proteasome system in nigrostriatal toxicity, in: annals of the New York Academy of Sciences. Blackwell Publishing Inc. 84–89. https://doi.org/10.1196/annals.1369.007.

Fornai, F., Longone, P., Ferrucci, M., Lenzi, P., Isidoro, C., Ruggieri, S., Paparelli, A., 2008. Autophagy and amyotrophic lateral sclerosis: the multiple roles of lithium. Autophagy 4, 527–530. https://doi.org/10.4161/auto.5923.

Fowler, J.S., Volkow, N.D., Logan, J., Alexoff, D., Telang, F., Wang, G.J., Wong, C., Ma, Y., Kriplani, A., Pradhan, K., Schlyer, D., Jayne, M., Hubbard, B., Carter, P., Warner, D., King, P., Shea, C., Xu, Y., Muench, L., Apelskog, K., 2008. Fast uptake and long-lasting binding of methamphetamine in the human brain: comparison with cocaine. Neuroimage 43, 756–763. https://doi.org/10.1016/j.neuroimage.2008.07.020.

Frank, M.G., Adhikary, S., Sobesky, J.L., Weber, M.D., Watkins, L.R., Maier, S.F., 2016. The danger-associated molecular pattern HMGB1 mediates the neuroinflammatory effects of methamphetamine. Brain Behav. Immun. 51, 99–108. https://doi.org/10.1016/j.bbi.2015.08.001.

Furman, C.A., Lo, C.B., Stokes, S., Esteban, J.A., Gnegy, M.E., 2009. Rab 11 regulates constitutive dopamine transporter trafficking and function in N2A neuroblastoma cells. Neurosci. Lett. 463, 78–81. https://doi.org/10.1016/j.neulet.2009.07.049.

Furuya, T., Kim, M., Lipinski, M., Li, J., Kim, D., Lu, T., Shen, Y., Rameh, L., Yankner, B., Tsai, L.H., Yuan, J., 2010. Negative regulation of Vps34 by cdk mediated phosphorylation. Mol. Cell 38, 500–511. https://doi.org/10.1016/j.molcel.2010.05.009.

Fuxe, K., Dahlström, A.B., Jonsson, G., Marcellino, D., Guescini, M., Dam, M., Manger, P., Agnati, L., 2010. The discovery of central monoamine neurons gave volume transmission to the wired brain. Prog. Neurobiol. 90, 82–100. https://doi.org/10.1016/j.pneurobio.2009.10.012.

Gangarossa, G., Ceolin, L., Paucard, A., Lerner-Natoli, M., Perroy, J., Fagni, L., Valjent, E., 2014. Repeated stimulation of dopamine D1-like receptor and hyperactivation of mTOR signaling lead to generalized seizures, altered dentate gyrus plasticity, and memory deficits. Hippocampus 24, 1466–1481. https://doi.org/10.1002/hipo.22327.

García-Sanz, P., Orgaz, L., Fuentes, J.M., Vicario, C., Moratalla, R., 2018. Cholesterol and multilamellar bodies: lysosomal dysfunction in GBA-Parkinson disease. Autophagy 14, 717–718. https://doi.org/10.1080/15548627.2018.1427396.

García-Sanz, P., Aerts, J., Moratalla, R., 2020. The role of cholesterol in α-Synuclein and Lewy Body Pathology in GBA1 parkinson's disease. Mov. Disord. https://doi.org/10.1002/mds.28396.

Gassen, N.C., Hartmann, J., Zschocke, J., Stepan, J., Hafner, K., Zellner, A., Kirmeier, T., Kollmannsberger, L., Wagner, K.V., Dedic, N., Balsevich, G., Deussing, J.M., Kloiber, S., Lucae, S., Holsboer, F., Eder, M., Uhr, M., Ising, M., Schmidt, M.V., Rein, T., 2014. Association of FKBP51 with priming of autophagy pathways and mediation of antidepressant treatment response: evidence in cells, mice, and humans. PLoS Med. 11 (11), e1001755 https://doi.org/10.1371/journal.pmed.1001755.

Gassen, N.C., Rein, T., 2019. Is there a role of autophagy in depression and antidepressant action? Front. Psychiatry. 10, 337. https://doi.org/10.3389/fpsyt.2019.00337.

Gassen, N.C., Hartmann, J., Schmidt, M.V., Rein, T., 2015. FKBP5/FKBP51 enhances autophagy to synergize with antidepressant action. Autophagy 11, 578–580. https://doi.org/10.1080/15548627.2015.1017224.

Geisler, S., Holmström, K.M., Treis, A., Skujat, D., Weber, S.S., Fiesel, F.C., Kahle, P.J., Springer, W., 2010a. The PINK1/Parkin-mediated mitophagy is compromised by PD-associated mutations. Autophagy 6, 871–878. https://doi.org/10.4161/auto.6.7.13286.

Geisler, S., Holmström, K.M., Skujat, D., Fiesel, F.C., Rothfuss, O.C., Kahle, P.J., Springer, W., 2010b. PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat. Cell Biol. 12, 119–131. https://doi.org/10.1038/ncb2012.

Gesi, M., Santinami, A., Ruffoli, R., Conti, G., Fornai, F., 2001. Novel aspects of dopamine oxidative metabolism (Confounding outcomes take place of certainties). Pharmacol. Toxicol. 89, 217–224. https://doi.org/10.1034/j.1600-0773.2001.d01-151.x.

Glasner-Edwards, S., Mooney, L.J., 2014. Methamphetamine psychosis: epidemiology and management. CNS Drugs 28, 1115–1126. https://doi.org/10.1007/s40263-014-0209-8.

Glasner-Edwards, S., Mooney, L.J., Marinelli-Casey, P., Hillhouse, M., Ang, A., Rawson, R., 2011. Bulimia nervosa among methamphetamine dependent adults: association with outcomes three years after treatment. Eat. Disord. 19, 259–269. https://doi.org/10.1080/10640266.2011.566149.

Gluck, M.R., Moy, L.Y., Jayatilleke, E., Hogan, K.A., Manzino, L., Sonsalla, P.K., 2001. Parallel increases in lipid and protein oxidative markers in several mouse brain regions after methamphetamine treatment. J. Neurochem. 79, 152–160. https://doi.org/10.1046/j.1471-4159.2001.00549.x.

Godino, A., Jayanthi, S., Cadet, J.L., 2015. Epigenetic landscape of amphetamine and methamphetamine addiction in rodents. Epigenetics 10, 574–580. https://doi.org/10.1080/15592294.2015.1055441.

Gonçalves, J., Martins, T., Ferreira, R., Milhazes, N., Borges, F., Ribeiro, C.F., Malva, J.O., Macedo, T.R., Silva, A.P., 2008. Methamphetamine-induced early increase of IL-6 and TNF-α mRNA expression in the mouse brain. Ann. N. Y. Acad. Sci. 1139, 103–111. https://doi.org/10.1196/annals.1432.043.

Gowrisankaran, S., Houy, S., del Castillo, J.G.P., Steubler, V., Gelker, M., Kroll, J., Pinheiro, P.S., Schwitters, D., Halbsgut, N., Pechstein, A., van Weering, J.R.T., Maritzen, T., Haucke, V., Raimundo, N., Sørensen, J.B., Milosevic, I., 2020. Endophilin-A coordinates priming and fusion of neurosecretory vesicles via intersectin. Nat. Commun. 11, 1266. https://doi.org/10.1038/s41467-020-14993-8.

Granado, N., Ares-Santos, S., O'Shea, E., Vicario-Abejón, C., Colado, M.I., Moratalla, R., 2010. Selective vulnerability in striosomes and in the nigrostriatal dopaminergic pathway after methamphetamine administration: early loss of TH in striosomes after methamphetamine. Neurotox. Res. 18, 48–58. https://doi.org/10.1007/s12640-009-9106-1.

Granado, N., Lastres-Becker, I., Ares-Santos, S., Oliva, I., Martin, E., Cuadrado, A., Moratalla, R., 2011. Nrf2 deficiency potentiates methamphetamine-induced dopaminergic axonal damage and gliosis in the striatum. Glia 59, 1850–1863. https://doi.org/10.1002/glia.21229.

Guillot, T.S., Shepherd, K.R., Richardson, J.R., Wang, M.Z., Li, Y., Emson, P.C., Miller, G. W., 2008. Reduced vesicular storage of dopamine exacerbates methamphetamine-induced neurodegeneration and astrogliosis. J. Neurochem. 106, 2205–2217. https://doi.org/10.1111/j.1471-4159.2008.05568.x.

Gulbins, A., Schumacher, F., Becker, K.A., Wilker, B., Soddemann, M., Boldrin, F., Müller, C.P., Edwards, M.J., Goodman, M., Caldwell, C.C., Kleuser, B., Kornhuber, J., Szabo, I., Gulbins, E., 2018. Antidepressants act by inducing autophagy controlled by sphingomyelin–ceramide. Mol. Psychiatry 23, 2324–2346. https://doi.org/10.1038/s41380-018-0090-9.

Guo, D., Xie, J., Zhao, J., Huang, T., Guo, X., Song, J., 2018. Resveratrol protects early brain injury after subarachnoid hemorrhage by activating autophagy and inhibiting apoptosis mediated by the Akt/mTOR pathway. Neuroreport 29, 368–379. https://doi.org/10.1097/WNR.0000000000000975.

Gupta, V.K., Pech, U., Bhukel, A., Fulterer, A., Ender, A., Mauermann, S.F., Andlauer, T.F. M., Antwi-Adjei, E., Beuschel, C., Thriene, K., Maglione, M., Quentin, C., Bushow, R., Schwärzel, M., Mielke, T., Madeo, F., Dengjel, J., Fiala, A., Sigrist, S.J., 2016. Spermidine suppresses age-associated memory impairment by preventing adverse increase of presynaptic active zone size and release. PLoS Biol. 14, e1002563 https://doi.org/10.1371/journal.pbio.1002563.

Hadamitzky, M., McCunney, S., Markou, A., Kuczenski, R., 2012. Development of stereotyped behaviors during prolonged escalation of methamphetamine self-administration in rats. Psychopharmacology (Berl.) 223, 259–269. https://doi.org/10.1007/s00213-012-2713-1.

Han, X., Sun, S., Sun, Y., Song, Q., Zhu, J., Song, N., Chen, M., Sun, T., Xia, M., Ding, J., Lu, M., Yao, H., Hu, G., 2019. Small molecule-driven NLRP3 inflammation inhibition via interplay between ubiquitination and autophagy: implications for Parkinson disease. Autophagy 15, 1860–1881. https://doi.org/10.1080/15548627.2019.1596481.

Han, S., Jeong, Y.Y., Sheshadri, P., Cai, Q., 2020. Mitophagy coordination with retrograde transport ensures the integrity of synaptic mitochondria. Autophagy 16, 1925–1927. https://doi.org/10.1080/15548627.2020.1810919.

Hara, T., Nakamura, K., Matsui, M., Yamamoto, A., Nakahara, Y., Suzuki-Migishima, R., Yokoyama, M., Mishima, K., Saito, I., Okano, H., Mizushima, N., 2006. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature 441, 885–889. https://doi.org/10.1038/nature04724.

He, X., Yuan, W., Li, Z., Hou, Y., Liu, F., Feng, J., 2018. 6-Hydroxydopamine induces autophagic flux dysfunction by impairing transcription factor EB activation and lysosomal function in dopaminergic neurons and SH-SY5Y cells. Toxicol. Lett. 283, 58–68. https://doi.org/10.1016/j.toxlet.2017.11.017.

Hernandez, D., Torres, C.A., Setlik, W., Cebrián, C., Mosharov, E.V., Tang, G., Cheng, H. C., Kholodilov, N., Yarygina, O., Burke, R.E., Gershon, M., Sulzer, D., 2012. Regulation of presynaptic neurotransmission by macroautophagy. Neuron 74, 277–284. https://doi.org/10.1016/j.neuron.2012.02.020.

Hirata, H., Cadet, J.L., 1997. p53-knockout mice are protected against the long-term effects of methamphetamine on dopaminergic terminals and cell bodies. J. Neurochem. 69, 780–790. https://doi.org/10.1046/j.1471-4159.1997.69020780.x.

Hoffman, W.F., Moore, M., Templin, R., McFarland, B., Hitzemann, R.J., Mitchell, S.H., 2006. Neuropsychological function and delay discounting in methamphetamine-dependent individuals. Psychopharmacology 188, 162–170. https://doi.org/10.1007/s00213-006-0494-0.

Homer, B.D., Solomon, T.M., Moeller, R.W., Mascia, A., DeRaleau, L., Halkitis, P.N., 2008. Methamphetamine abuse and impairment of social functioning: a review of

the underlying neurophysiological causes and behavioral implications. Psychol. Bull. 134, 301–310. https://doi.org/10.1037/0033-2909.134.2.301.

Hong, W.C., Amara, S.G., 2013. Differential targeting of the dopamine transporter to recycling or degradative pathways during amphetamine-or PKC-regulated endocytosis in dopamine neurons. FASEB J. 27, 2995–3007. https://doi.org/10.1096/fj.12-218727.

Howes, O.D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., Kapur, S., 2012. The nature of dopamine dysfunction in schizophrenia and what this means for treatment: meta-analysisof imaging studies. Arch. Gen. Psychiatry 69, 776–786. https://doi.org/10.1001/archgenpsychiatry.2012.169.

Hu, Z.Y., Chen, B., Zhang, J.P., Ma, Y.Y., 2017. Up-regulation of autophagy-related gene 5 (ATG5) protects dopaminergic neurons in a zebrafish model of Parkinson's disease. J. Biol. Chem. 292, 18062–18074. https://doi.org/10.1074/jbc.M116.764795.

Huang, S.P., Chien, J.Y., Tsai, R.K., 2015. Ethambutol induces impaired autophagic flux and apoptosis in the rat retina. DMM Dis. Model. Mech. 8, 977–987. https://doi.org/10.1242/dmm.019737.

Huang, S.H., Wu, W.R., Lee, L.M., Huang, P.R., Chen, J.C., 2018. mTOR signaling in the nucleus accumbens mediates behavioral sensitization to methamphetamine. Prog. Neuro-Psychopharmacology Biol. Psychiatry 86, 331–339. https://doi.org/10.1016/j.pnpbp.2018.03.017.

Hui, K.K., Tanaka, M., 2019. Autophagy links MTOR and GABA signaling in the brain. Autophagy 15, 1848–1849. https://doi.org/10.1080/15548627.2019.1637643.

Hunn, B.H.M., Vingill, S., Threlfell, S., Alegre-Abarrategui, J., Magdelyns, M., Deltheil, T., Bengoa-Vergniory, N., Oliver, P.L., Cioroch, M., Doig, N.M., Bannerman, D.M., Cragg, S.J., Wade-Martins, R., 2019. Impairment of macroautophagy in dopamine neurons has opposing effects on parkinsonian pathology and behavior. Cell Rep. 29, 920–931. https://doi.org/10.1016/j.celrep.2019.09.029 e7.

Ichimura, Y., Waguri, S., Sou, Yshin, Kageyama, S., Hasegawa, J., Ishimura, R., Saito, T., Yang, Y., Kouno, T., Fukutomi, T., Hoshii, T., Hirao, A., Takagi, K., Mizushima, T., Motohashi, H., Lee, M.S., Yoshimori, T., Tanaka, K., Yamamoto, M., Komatsu, M., 2013. Phosphorylation of p62 activates the Keap1-Nrf2 pathway during selective autophagy. Mol. Cell 51, 618–631. https://doi.org/10.1016/j.molcel.2013.08.003.

Iritani, S., Sekiguchi, H., Habuchi, C., Torii, Y., Yamada, S., Waki, Y., Noda, Y., Furukawa, H., Nabeshima, T., Ozaki, N., 2010. Immunohistochemical study of vesicle monoamine transporter 2 in the hippocampal formation of PCP-treated mice. Neurosci. Res. 68, 125–130. https://doi.org/10.1016/j.neures.2010.06.005.

Jakel, R.J., Maragos, W.F., 2000. Neuronal cell death in Huntington's disease: a potential role for dopamine. Trends Neurosci. 23, 239–245. https://doi.org/10.1016/S0166-2236(00)01568-X.

Jayanthi, S., Ladenheim, B., Cadet, J.L., 1998. Methamphetamine-induced changes in antioxidant enzymes and lipid peroxidation in Copper/Zinc-Superoxide dismutase transgenic mice. Ann. N. Y. Acad. Sci. 844, 92–102. https://doi.org/10.1111/j.1749-6632.1998.tb08224.x.

Jayanthi, S., Deng, X., Bordelon, M., McCoy, M.T., Cadet, J.L., 2001. Methamphetamine causes differential regulation of pro-death and anti-death Bcl-2 genes in the mouse neocortex. FASEB J. 15, 1745–1752. https://doi.org/10.1096/fj.01-0025com.

Jayanthi, S., Deng, X., Noailles, P.A., Ladenheim, B., Cadet, J.L., 2004. Methamphetamine induces neuronal apoptosis via cross-talks between endoplasmic reticulum and mitochondria-dependent death cascades. FASEB J. 18, 238–251. https://doi.org/10.1096/fj.03-0295com.

Jayanthi, S., Deng, X., Ladenheim, B., McCoy, M.T., Cluster, A., Cai, N.S., Cadet, J.L., 2005. Calcineurin/NFAT-induced up-regulation of the Fas ligand/Fas death pathway is involved in methamphetamine-induced neuronal apoptosis. Proc. Natl. Acad. Sci. U. S. A. 102, 868–873. https://doi.org/10.1073/pnas.0404990102.

Jiao, D., Liu, Y., Li, X., Liu, J., Zhao, M., 2015. The role of the GABA system in amphetamine-type stimulant use disorders. Front. Cell. Neurosci. 9, 162. https://doi.org/10.3389/fncel.2015.00162.

Jin, X., Sasamoto, K., Nagai, J., Yamazaki, Y., Saito, K., Goshima, Y., Inoue, T., Ohshima, T., 2016. Phosphorylation of CRMP2 by Cdk5 regulates dendritic spine development of cortical neuron in the mouse hippocampus. Neural Plast. 2016, 6790743 https://doi.org/10.1155/2016/6790743.

Jinsmaa, Y., Isonaka, R., Sharabi, Y., Goldstein, D.S., 2020. 3,4-Dihydroxyphenylacetaldehyde is more efficient than dopamine in oligomerizing and quinonizing a-synuclein. J. Pharmacol. Exp. Ther. 372, 157–165. https://doi.org/10.1124/JPET.119.262246.

Kageyama, S., Sou, Y.S., Uemura, T., Kametaka, S., Saito, T., Ishimura, R., Kouno, T., Bedford, L., Mayer, R.J., Lee, M.S., Yamamoto, M., Waguri, S., Tanaka, K., Komatsu, M., 2014. Proteasome dysfunction activates autophagy and the Keap1-Nrf2 pathway. J. Biol. Chem. 289, 24944–24955. https://doi.org/10.1074/jbc.M114.580357.

Kamada, Y., Yoshino, K., Kondo, C., Kawamata, T., Oshiro, N., Yonezawa, K., Ohsumi, Y., 2010. Tor directly controls the Atg1 kinase complex to regulate autophagy. Mol. Cell. Biol. 30, 1049–1058. https://doi.org/10.1128/mcb.01344-09.

Kang, S.S., Liu, X., Ahn, E.H., Xiang, J., Manfredsson, F.P., Yang, X., Luo, H.R., Liles, L.C., Weinshenker, D., Ye, K., 2020. Norepinephrine metabolite DOPEGAL activates AEP and pathological Tau aggregation in locus coeruleus. J. Clin. Invest. 130, 422–437. https://doi.org/10.1172/JCI130513.

Kara, N.Z., Toker, L., Agam, G., Anderson, G.W., Belmaker, R.H., Einat, H., 2013. Trehalose induced antidepressant-like effects and autophagy enhancement in mice. Psychopharmacology (Berl.) 229, 367–375. https://doi.org/10.1007/s00213-013-3119-4.

Kara, N.Z., Flaisher-Grinberg, S., Anderson, G.W., Agam, G., Einat, H., 2018. Mood-stabilizing effects of rapamycin and its analog temsirolimus: relevance to autophagy. Behav. Pharmacol. 29, 379–384. https://doi.org/10.1097/FBP.0000000000000334.

Kaushik, S., Cuervo, A.M., 2012. Chaperone-mediated autophagy: a unique way to enter the lysosome world. Trends Cell Biol. 22, 407–417. https://doi.org/10.1016/j.tcb.2012.05.006.

Kedracka-Krok, S., Swiderska, B., Jankowska, U., Skupien-Rabian, B., Solich, J., Buczak, K., Dziedzicka-Wasylewska, M., 2015. Clozapine influences cytoskeleton structure and calcium homeostasis in rat cerebral cortex and has a different proteomic profile than risperidone. J. Neurochem. 132, 657–676. https://doi.org/10.1111/jnc.13007.

Khoshsirat, S., Khoramgah, M.S., Mahmoudiasl, G.R., Rezaei-Tavirani, M., Abdollahifar, M.A., Tahmasebinia, F., Darabi, S., Niknazar, S., Abbaszadeh, H.A., 2020. LC3 and ATG5 overexpression and neuronal cell death in the prefrontal cortex of postmortem chronic methamphetamine users. J. Chem. Neuroanat. 107, 101802 https://doi.org/10.1016/j.jchemneu.2020.101802.

Kim, J.Y., Duan, X., Liu, C.Y., Jang, M.H., Guo, J.U., Pow-anpongkul, N., Kang, E., Song, H., Ming, Gli, 2009. DISC1 regulates new neuron development in the adult brain via modulation of AKT-mTOR signaling through KIAA1212. Neuron 63, 761–773. https://doi.org/10.1016/j.neuron.2009.08.008.

Kim, Y.D., Jeong II, E., Nah, J., Yoo, S.-M., Lee, W.J., Kim, Y., Moon, S., Hong, S.-H., Jung, Y.-K., 2017. Pimozide reduces toxic forms of tau in TauC3 mice via 5′ adenosine monophosphate-activated protein kinase-mediated autophagy. J. Neurochem. 142, 734–746. https://doi.org/10.1111/jnc.14109.

Kim, S.H., Park, S., Yu, H.S., Ko, K.H., Park, H.G., Kim, Y.S., 2018. The antipsychotic agent clozapine induces autophagy via the AMPK-ULK1-Beclin1 signaling pathway in the rat frontal cortex. Prog. Neuro-Psychopharmacology Biol. Psychiatry 81, 96–104. https://doi.org/10.1016/j.pnpbp.2017.10.012.

Kitamura, O., 2009. Detection of methamphetamine neurotoxicity in forensic autopsy cases. Leg. Med. Tokyo (Tokyo) 11 (Suppl 1), S63–S65. https://doi.org/10.1016/j.legalmed.2009.01.003.

Kitamura, O., Tokunaga, I., Gotohda, T., Kubo, S., 2007. Immunohistochemical investigation of dopaminergic terminal markers and caspase-3 activation in the striatum of human methamphetamine users. Int. J. Legal Med. 121, 163–168. https://doi.org/10.1007/s00414-006-0087-9.

Klionsky, D.J., Abdelmohsen, K., Abe, A., Abedin, M.J., et al., 2016. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. https://doi.org/10.1080/15548627.2015.1100356.

Kobeissy, F.H., Warren, M.W., Ottens, A.K., Sadasivan, S., Zhang, Z., Gold, M.S., Wang, K.K.W., 2008. Psychoproteomic analysis of rat cortex following acute methamphetamine exposure. J. Proteome Res. 7, 1971–1983. https://doi.org/10.1021/pr800029h.

Komatsu, M., Waguri, S., Chiba, T., Murata, S., Iwata, J.I., Tanida, I., Ueno, T., Koike, M., Uchiyama, Y., Kominami, E., Tanaka, K., 2006. Loss of autophagy in the central nervous system causes neurodegeneration in mice. Nature 441, 880–884. https://doi.org/10.1038/nature04723.

Komatsu, M., Qing, J.W., Holstein, G.R., Friedrich, V.L., Iwata, J.I., Kominami, E., Chait, B.T., Tanaka, K., Yue, Z., 2007. Essential role for autophagy protein Atg7 in the maintenance of axonal homeostasis and the prevention of axonal degeneration. Proc. Natl. Acad. Sci. U. S. A. 104, 14489–14494. https://doi.org/10.1073/pnas.0701311104.

Krashia, P., Nobili, A., D'amelio, M., 2019. Unifying hypothesis of dopamine neuron loss in neurodegenerative diseases: focusing on alzheimer's disease. Front. Mol. Neurosci. 12, 123. https://doi.org/10.3389/fnmol.2019.00123.

Krasnova, I.N., Justinova, Z., Ladenheim, B., Jayanthi, S., McCoy, M.T., Barnes, C., Warner, J.E., Goldberg, S.R., Cadet, J.L., 2010. Methamphetamine self-administration is associated with persistent biochemical alterations in striatal and cortical dopaminergic terminals in the rat. PLoS One 5, e8790. https://doi.org/10.1371/journal.pone.0008790.

Krasnova, I.N., Justinova, Z., Cadet, J.L., 2016. Methamphetamine addiction: involvement of CREB and neuroinflammatory signaling pathways. Psychopharmacology (Berl.) 233, 1945–1962. https://doi.org/10.1007/s00213-016-4235-8.

Kulbe, J.R., Mulcahy Levy, J.M., Coultrap, S.J., Thorburn, A., Ulrich Bayer, K., 2014. Excitotoxic glutamate insults block autophagic flux in hippocampal neurons. Brain Res. 1542, 12–19. https://doi.org/10.1016/j.brainres.2013.10.032.

Lai, M., Yao, H., Ali Shah, S.Z., Wu, W., Wang, D., Zhao, Y., Wang, L., Zhou, X., Zhao, D., Yang, L., 2018. The NLRP3-Caspase 1 inflammasome negatively regulates autophagy via TLR4-TRIF in prion peptide-infected microglia. Front. Aging Neurosci. 10, 116. https://doi.org/10.3389/fnagi.2018.00116.

Lai, C.C., Fang, C., Kuo, C.Y., Wu, Y.W., Lin, H.H., 2020. Activation of mglur5 and nmda receptor pathways in the rostral ventrolateral medulla as a central mechanism for methamphetamine-induced pressor effect in rats. Biomolecules 10, 149. https://doi.org/10.3390/biom10010149.

Larsen, K.E., Fon, E.A., Hastings, T.G., Edwards, R.H., Sulzer, D., 2002. Methamphetamine-induced degeneration of dopaminergic neurons involves autophagy and upregulation of dopamine synthesis. J. Neurosci. 22, 8951–8960. https://doi.org/10.1523/jneurosci.22-20-08951.2002.

Laruelle, M., Abi-Dargham, A., Gil, R., Kegeles, L., Innis, R., 1999. Increased dopamine transmission in schizophrenia: relationship to illness phases. Biol. Psychiatry 46, 56–72. https://doi.org/10.1016/S0006-3223(99)00067-0.

LaVoie, M.J., Hastings, T.G., 1999. Dopamine quinone formation and protein modification associated with the striatal neurotoxicity of methamphetamine: evidence against a role for extracellular dopamine. J. Neurosci. 19, 1484–1491. https://doi.org/10.1523/jneurosci.19-04-01484.1999.

LaVoie, M.J., Card, J.P., Hastings, T.G., 2004. Microglial activation precedes dopamine terminal pathology in methamphetamine-induced neurotoxicity. Exp. Neurol. 187, 47–57. https://doi.org/10.1016/j.expneurol.2004.01.010.

Lazzeri, G., Lenzi, P., Gesi, M., Ferrucci, M., Fulceri, F., Ruggieri, S., Bruno, V., Fornai, F., 2006. In PC12 cells neurotoxicity induced by methamphetamine is related to proteasome inhibition. Ann. N. Y. Acad. Sci. 1074, 174–177. https://doi.org/10.1196/annals.1369.017.

Lazzeri, G., Lenzi, P., Busceti, C.L., Ferrucci, M., Falleni, A., Bruno, V., Paparelli, A., Fornai, F., 2007. Mechanisms involved in the formation of dopamine-induced intracellular bodies within striatal neurons. J. Neurochem. 101, 1414–1427. https://doi.org/10.1111/j.1471-4159.2006.04429.x.

Lazzeri, G., Biagioni, F., Fulceri, F., Busceti, C.L., Scavuzzo, M.C., Ippolito, C., Salvetti, A., Lenzi, P., Fornai, F., 2018. MTOR modulates methamphetamine-induced toxicity through cell clearing systems. Oxid. Med. Cell. Longev. 2018, 6124745 https://doi.org/10.1155/2018/6124745.

Lebel, M., Patenaude, C., Allyson, J., Massicotte, G., Cyr, M., 2009. Dopamine D1 receptor activation induces tau phosphorylation via cdk5 and GSK3 signaling pathways. Neuropharmacology 57, 392–402. https://doi.org/10.1016/j.neuropharm.2009.06.041.

Lee, W., Kim, S.H., 2019. Autophagy at synapses in neurodegenerative diseases. Arch. Pharm. Res. 42, 407–415. https://doi.org/10.1007/s12272-019-01148-7.

Lee, Y., Hamamura, T., Ohashi, K., Fujiwara, Y., Kuroda, S., 1999. The effect of lithium on methamphetamine-induced regional Fos protein expression in the rat brain. Neuroreport 10, 895–900. https://doi.org/10.1097/00001756-199904060-00001.

Lee, B., London, E.D., Poldrack, R.A., Farahi, J., Nacca, A., Monterosso, J.R., Mumford, J. A., Bokarius, A.V., Dahlbom, M., Mukherjee, J., Bilder, R.M., Brody, A.L., Mandelkern, M.A., 2009. Striatal dopamine D2/D3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. J. Neurosci. 29, 14734–14740. https://doi.org/10.1523/JNEUROSCI.3765-09.2009.

Lee, H., Joo, J., Nah, S.S., Kim, J.W., Kim, H.K., Kwon, J.T., Lee, H.Y., Kim, Y.O., Kim, H. J., 2015. Changes in Dpysl2 expression are associated with prenatally stressed rat offspring and susceptibility to schizophrenia in humans. Int. J. Mol. Med. 35, 1574–1586. https://doi.org/10.3892/ijmm.2015.2161.

Lenzi, P., Marongiu, R., Falleni, A., Gelmetti, V., Busceti, C.L., Michiorri, S., Valente, E. M., Fornai, F., 2012. Ultrastructural analysis of genetic modulation of PINK1. Arch. Ital. Biol. 150, 194–217. https://doi.org/10.4449/AIB.V150I2/3.1417.

Leriche, L., Diaz, J., Sokoloff, P., 2004. Dopamine and glutamate dysfunctions in schizophrenia: role of the dopamine D3 receptor. Neurotox. Res. 6, 63–71. https://doi.org/10.1007/BF03033298.

Li, F.C.H., Yen, J.C., Chan, S.H.H., Chang, A.Y.W., 2012. Bioenergetics failure and oxidative stress in brain stem mediates cardiovascular collapse associated with fatal methamphetamine intoxication. PLoS One 7, e30589. https://doi.org/10.1371/journal.pone.0030589.

Li, X., Rubio, F.J., Zeric, T., Bossert, J.M., Kambhampati, S., Cates, H.M., Kennedy, P.J., Liu, Q.R., Cimbro, R., Hope, B.T., Nestler, E.J., Shaham, Y., 2015. Incubation of methamphetamine craving is associated with selective increases in expression of Bdnf and Trkb, glutamate receptors, and epigenetic enzymes in cue-activated fos-expressing dorsal striatal neurons. J. Neurosci. 35, 8232–8244. https://doi.org/10.1523/JNEUROSCI.1022-15.2015.

Li, Z., Schulze, R.J., Weller, S.G., Krueger, E.W., Schott, M.B., Zhang, X., Casey, C.A., Liu, J., Stöckli, J., James, D.E., McNiven, M.A., 2016. A novel rab10-EHBP1-EHD2 complex essential for the autophagic engulfment of lipid droplets. Sci. Adv. 2, 1601470 https://doi.org/10.1126/sciadv.1601470.

Li, L., Chen, S., Wang, Y., Yue, X., Xu, J., Xie, W., Qiu, P., Liu, C., Wang, A., Wang, H., 2017. Role of GSK3β/α-synuclein axis in methamphetamine-induced neurotoxicity in PC12 cells. Toxicol. Res. (Camb). 7, 221–234. https://doi.org/10.1039/c7tx00189d.

Li, C., Wang, X., Li, X., Qiu, K., Jiao, F., Liu, Yidan, Kong, Q., Liu, Yan, Wu, Y., 2019. Proteasome inhibition activates autophagy-lysosome pathway associated with TFEB dephosphorylation and nuclear translocation. Front. Cell Dev. Biol. 7, 170. https://doi.org/10.3389/fcell.2019.00170.

Limanaqi, F., Biagioni, F., Gambardella, S., Ryskalin, L., Fornai, F., 2018a. Interdependency between autophagy and synaptic vesicle trafficking: implications for dopamine release. Front. Mol. Neurosci. 11, 299. https://doi.org/10.3389/fnmol.2018.00299.

Limanaqi, F., Gambardella, S., Biagioni, F., Busceti, C.L., Fornai, F., 2018b. Epigenetic effects induced by methamphetamine and methamphetamine-dependent oxidative stress. Oxid. Med. Cell. Longev. 2018, 4982453 https://doi.org/10.1155/2018/4982453.

Limanaqi, F., Biagioni, F., Busceti, C.L., Ryskalin, L., Fornai, F., 2019. The effects of proteasome on baseline and methamphetamine-dependent dopamine transmission. Neurosci. Biobehav. Rev. 102, 308–317. https://doi.org/10.1016/j.neubiorev.2019.05.008.

Limanaqi, F., Biagioni, F., Gambardella, S., Familiari, P., Frati, A., Fornai, F., 2020a. Promiscuous roles of autophagy and proteasome in neurodegenerative proteinopathies. Int. J. Mol. Sci. 21, 3028. https://doi.org/10.3390/ijms21083028.

Limanaqi, F., Busceti, C.L., Biagioni, F., Fornai, F., Puglisi-Allegra, S., 2020b. Autophagy-based hypothesis on the role of brain catecholamine response during stress. Front. Psychiatry 11, 993. https://doi.org/10.3389/fpsyt.2020.569248.

Lin, M., Chandramani-Shivalingappa, P., Jin, H., Ghosh, A., Anantharam, V., Ali, S., Kanthasamy, A.G., Kanthasamy, A., 2012. Methamphetamine-induced neurotoxicity linked to ubiquitin-proteasome system dysfunction and autophagy-related changes that can be modulated by protein kinase C delta in dopaminergic neuronal cells. Neuroscience 210, 308–332. https://doi.org/10.1016/j.neuroscience.2012.03.004.

Liu, B., Dluzen, D.E., 2006. Effect of estrogen upon methamphetamine-induced neurotoxicity within the impaired nigrostriatal dopaminergic system. Synapse 60, 354–361. https://doi.org/10.1002/syn.20307.

Liu, Y., Pham, X., Zhang, L., Chen, Plung, Burzynski, G., McGaughey, D.M., He, S., McGrath, J.A., Wolyniec, P., Fallin, M.D., Pierce, M.S., McCallion, A.S., Pulver, A.E., Avramopoulos, D., Valle, D., 2015. Functional variants in DPYSL2 sequence increase risk of schizophrenia and suggest a link to mTOR signaling. G3 Genes, Genomes, Genet. 5, 61–72. https://doi.org/10.1534/g3.114.015636.

Liu, C.H., Ren, J., Liu, P.K., 2016. Amphetamine manipulates monoamine oxidase-A level and behavior using theranostic aptamers of transcription factors AP-1/NF-kB. J. Biomed. Sci. 23, 21. https://doi.org/10.1186/s12929-016-0239-2.

Loder, M.K., Melikian, H.E., 2003. The dopamine transporter constitutively internalizes and recycles in a protein kinase C-regulated manner in stably transfected PC12 cell lines. J. Biol. Chem. 278, 22168–22174. https://doi.org/10.1074/jbc.M301845200.

Luderman, K.D., Chen, R., Ferris, M.J., Jones, S.R., Gnegy, M.E., 2015. Protein kinase C beta regulates the D2-Like dopamine autoreceptor. Neuropharmacology 89, 335–341. https://doi.org/10.1016/j.neuropharm.2014.10.012.

Ma, X.M., Blenis, J., 2009. Molecular mechanisms of mTOR-mediated translational control. Nat. Rev. Mol. Cell Biol. 10, 307–318. https://doi.org/10.1038/nrm2672.

Ma, J., Wan, J., Meng, J., Banerjee, S., Ramakrishnan, S., Roy, S., 2014. Methamphetamine induces autophagy as a pro-survival response against apoptotic endothelial cell death through the Kappa opioid receptor. Cell Death Dis. 5, e1099. https://doi.org/10.1038/cddis.2014.64.

Maggio, R., Aloisi, G., Silvano, E., Rossi, M., Millan, M.J., 2009. Heterodimerization of dopamine receptors: new insights into functional and therapeutic significance. Parkinsonism Relat. Disord. 15 (Suppl 4), S2–S7. https://doi.org/10.1016/S1353-8020(09)70826-0.

Mai, H.N., Sharma, N., Shin, E.-J., Nguyen, B.T., Nguyen, P.T., Jeong, J.H., Cho, E.-H., Lee, Y.J., Kim, N.H., Jang, C.-G., Nabeshima, T., Kim, H.-C., 2018. Exposure to far-infrared ray attenuates methamphetamine-induced impairment in recognition memory through inhibition of protein kinase C δ in male mice: Comparison with the antipsychotic clozapine. J. Neurosci. Res. 96, 1294–1310. https://doi.org/10.1002/jnr.24228.

Manji, H., Kato, T., Di Prospero, N.A., Ness, S., Beal, M.F., Krams, M., Chen, G., 2012. Impaired mitochondrial function in psychiatric disorders. Nat. Rev. Neurosci. 13, 293–307. https://doi.org/10.1038/nrn3229.

Markota, M., Sin, J., Pantazopoulos, H., Jonilionis, R., Berretta, S., 2014. Reduced dopamine transporter expression in the amygdala of subjects diagnosed with schizophrenia. Schizophr. Bull. 40, 984–991. https://doi.org/10.1093/schbul/sbu084.

Markov, D., Mosharov, E.V., Setlik, W., Gershon, M.D., Sulzer, D., 2008. Secretory vesicle rebound hyperacidification and increased quantal size resulting from prolonged methamphetamine exposure. J. Neurochem. 107, 1709–1721. https://doi.org/10.1111/j.1471-4159.2008.05737.x.

Marshall, J.F., O'Dell, S.J., 2012. Methamphetamine influences on brain and behavior: unsafe at any speed? Trends Neurosci. 35, 536–545. https://doi.org/10.1016/j.tins.2012.05.006.

Martinez-Vicente, M., Talloczy, Z., Kaushik, S., Massey, A.C., Mazzulli, J., Mosharov, E. V., Hodara, R., Fredenburg, R., Wu, D.C., Follenzi, A., Dauer, W., Przedborski, S., Ischiropoulos, H., Lansbury, P.T., Sulzer, D., Cuervo, A.M., 2008. Dopamine-modified α-synuclein blocks chaperone-mediated autophagy. J. Clin. Invest. 118, 777–778. https://doi.org/10.1172/JCI32806.

Masini, D., Bonito-Oliva, A., Bertho, M., Fisone, G., 2018. Inhibition of mTORC1 signaling reverts cognitive and affective deficits in a mouse model of Parkinson's disease. Front. Neurol. 9, 1. https://doi.org/10.3389/fneur.2018.00208.

Matsumoto, R.R., Seminerio, M.J., Turner, R.C., Robson, M.J., Nguyen, L., Miller, D.B., O'Callaghan, J.P., 2014. Methamphetamine-induced toxicity: an updated review on issues related to hyperthermia. Pharmacol. Ther. 144, 28–40. https://doi.org/10.1016/j.pharmthera.2014.05.001.

McCann, U.D., Kuwabara, H., Kumar, A., Palermo, M., Abbey, R., Brasic, J., Ye, W., Alexander, M., Dannals, R.F., Wong, D.F., Ricaurte, G.A., 2008. Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users. Synapse 62, 91–100. https://doi.org/10.1002/syn.20471.

McCutcheon, R.A., Abi-Dargham, A., Howes, O.D., 2019. Schizophrenia, dopamine and the striatum: from biology to symptoms. Trends Neurosci. 42, 205–220. https://doi.org/10.1016/j.tins.2018.12.004.

McFadden, L.M., Stout, K.A., Vieira-Brock, P.L., Allen, S.C., Nielsen, S.M., Wilkins, D.G., Hanson, G.R., Fleckenstein, A.E., 2012. Methamphetamine self-administration acutely decreases monoaminergic transporter function. Synapse 66, 240–245. https://doi.org/10.1002/syn.21506.

McFadden, L.M., Cordie, R., Livermont, T., Johansen, A., 2018. Behavioral and serotonergic changes in the frontal cortex following methamphetamine self-administration. Int. J. Neuropsychopharmacol. 21, 758–763. https://doi.org/10.1093/ijnp/pyy044.

McKetin, R., McLaren, J., Lubman, D.I., Hides, L., 2006. The prevalence of psychotic symptoms among methamphetamine users. Addiction 101, 1473–1478.

Mehrafza, S., Kermanshahi, S., Mostafidi, S., Motaghinejad, M., Motevalian, M., Fatima, S., 2019. Pharmacological evidence for lithium-induced neuroprotection against methamphetamine-induced neurodegeneration via Akt- 1/GSK3 and CREB-BDNF signaling pathways. Iran. J. Basic Med. Sci. 22, 856–865. https://doi.org/10.22038/ijbms.2019.30855.7442.

Merchant, K.M., Letter, A.A., Gibb, J.W., Hanson, G.R., 1988. Changes in the limbic neurotensin systems induced by dopaminergic drugs. Eur. J. Pharmacol. 153, 1–9. https://doi.org/10.1016/0014-2999(88)90581-X.

Meredith, C.W., Jaffe, C., Ang-Lee, K., Saxon, A.J., 2005. Implications of chronic methamphetamine use: a literature review. Harv. Rev. Psychiatry 13, 141–154. https://doi.org/10.1080/10673220591003605.

Merenlender-Wagner, A., Shemer, Z., Touloumi, O., Lagoudaki, R., Giladi, E., Andrieux, A., Grigoriadis, N.C., Gozes, I., 2014. New horizons in schizophrenia treatment: autophagy protection is coupled with behavioral improvements in a

mouse model of schizophrenia. Autophagy 10, 2324–2332. https://doi.org/10.4161/15548627.2014.984274.
Merenlender-Wagner, A., Malishkevich, A., Shemer, Z., Udawela, M., Gibbons, A., Scarr, E., Dean, B., Levine, J., Agam, G., Gozes, I., 2015. Autophagy has a key role in the pathophysiology of schizophrenia. Mol. Psychiatry 20, 126–132. https://doi.org/10.1038/mp.2013.174.
Miller, G.W., Erickson, J.D., Perez, J.T., Penland, S.N., Mash, D.C., Rye, D.B., Levey, A.I., 1999. Immunochemical analysis of vesicular monoamine transporter (VMAT2) protein in Parkinson's disease. Exp. Neurol. 156, 138–148. https://doi.org/10.1006/exnr.1998.7008.
Minoia, M., Boncoraglio, A., Vinet, J., Morelli, F.F., Brunsting, J.F., Poletti, A., Krom, S., Reits, E., Kampinga, H.H., Carra, S., 2014. BAG3 induces the sequestration of proteasomal clients into cytoplasmic puncta Implications for a proteasome-to-autophagy switch. Autophagy 10, 1603–1621. https://doi.org/10.4161/auto.29409.
Miyazaki, I., Asanuma, M., Diaz-Corrales, F.J., Fukuda, M., Kitaichi, K., Miyoshi, K., Ogawa, N., 2006. Methamphetamine-induced dopaminergic neurotoxicity is regulated by quinone formation-related molecules. FASEB J. 20, 571–573. https://doi.org/10.1096/fj.05-4996fje.
Miyazaki, M., Noda, Y., Mouri, A., Kobayashi, K., Mishina, M., Nabeshima, T., Yamada, K., 2013. Role of convergent activation of glutamatergic and dopaminergic systems in the nucleus accumbens in the development of methamphetamine psychosis and dependence. Int. J. Neuropsychopharmacol. 16, 1341–1350. https://doi.org/10.1017/S1461145712001356.
Mooslehner, K.A., Chan, P.M., Xu, W., Liu, L., Smadja, C., Humby, T., Allen, N.D., Wilkinson, L.S., Emson, P.C., 2001. Mice with very low expression of the vesicular monoamine transporter 2 gene survive into adulthood: potential mouse model for parkinsonism. Mol. Cell. Biol. 21, 5321–5331. https://doi.org/10.1128/MCB.21.16.5321-5331.2001.
Moratalla, R., Khairnar, A., Simola, N., Granado, N., García-Montes, J.R., Porceddu, P.F., Tizabi, Y., Costa, G., Morelli, M., 2017. Amphetamine-related drugs neurotoxicity in humans and in experimental animals: main mechanisms. Prog. Neurobiol. 155, 149–170. https://doi.org/10.1016/j.pneurobio.2015.09.011.
Morrow, B.A., Roth, R.H., Redmond, D.E., Elsworth, J.D., 2011. Impact of methamphetamine on dopamine neurons in primates is dependent on age: implications for development of Parkinson's disease. Neuroscience 189, 277–285. https://doi.org/10.1016/j.neuroscience.2011.05.046.
Moszczynska, A., Yamamoto, B.K., 2011. Methamphetamine oxidatively damages parkin and decreases the activity of 26S proteasome in vivo. J. Neurochem. 116, 1005–1017. https://doi.org/10.1111/j.1471-4159.2010.07147.x.
Muñoz, P., Huenchuguala, S., Paris, I., Segura-Aguilar, J., 2012. Dopamine oxidation and autophagy. Parkinsons Dis. 2012, 920953 https://doi.org/10.1155/2012/920953.
Murdoch, J.D., Rostosky, C.M., Gowrisankaran, S., Arora, A.S., Soukup, S.F., Vidal, R., Capece, V., Freytag, S., Fischer, A., Verstreken, P., Bonn, S., Raimundo, N., Milosevic, I., 2016. Endophilin-a deficiency induces the Foxo3a-Fbxo32 network in the brain and causes dysregulation of autophagy and the ubiquitin-proteasome system. Cell Rep. 17, 1071–1086. https://doi.org/10.1016/j.celrep.2016.09.058.
Nakai, T., Nagai, T., Wang, R., Yamada, S., Kuroda, K., Kaibuchi, K., Yamada, K., 2014. Alterations of GABAergic and dopaminergic systems in mutant mice with disruption of exons 2 and 3 of the Disc1 gene. Neurochem. Int. 74, 74–83. https://doi.org/10.1016/j.neuint.2014.06.009.
Namyen, J., Permpoonputtana, K., Nopparat, C., Tocharus, J., Tocharus, C., Govitrapong, P., 2020. Protective effects of melatonin on methamphetamine-induced blood–Brain barrier dysfunction in rat model. Neurotox. Res. 37, 640–660. https://doi.org/10.1007/s12640-019-00156-1.
Narita, M., Akai, H., Nagumo, Y., Sunagawa, N., Hasebe, K., Nagase, H., Kita, T., Hara, C., Suzuki, T., 2004. Implications of protein kinase C in the nucleus accumbens in the development of sensitization to methamphetamine in rats. Neuroscience 127, 941–948. https://doi.org/10.1016/j.neuroscience.2004.06.017.
Natale, G., Lenzi, P., Lazzeri, G., Falleni, A., Biagioni, F., Ryskalin, L., Fornai, F., 2015. Compartment-dependent mitochondrial alterations in experimental ALS, the effects of mitophagy and mitochondriogenesis. Front. Cell. Neurosci. 9, 434. https://doi.org/10.3389/fncel.2015.00434.
Neasta, J., Barak, S., Hamida, S.Ben, Ron, D., 2014. MTOR complex 1: a key player in neuroadaptations induced by drugs of abuse. J. Neurochem. 130, 172–184. https://doi.org/10.1111/jnc.12725.
Nestler, E.J., 2001. Molecular basis of long-term plasticity underlying addiction. Nat. Rev. Neurosci. 2, 119–128. https://doi.org/10.1038/35053570.
Niwa, M., Kamiya, A., Murai, R., Kubo, K., Gruber, A.J., Tomita, K., Lu, L., Tomisato, S., Jaaro-Peled, H., Seshadri, S., Hiyama, H., Huang, B., Kohda, K., Noda, Y., O'Donnell, P., Nakajima, K., Sawa, A., Nabeshima, T., 2010. Knockdown of DISC1 by in utero gene transfer disturbs postnatal dopaminergic maturation in the frontal cortex and leads to adult behavioral deficits. Neuron 65, 480–489. https://doi.org/10.1016/j.neuron.2010.01.019.
Northrop, N.A., Yamamoto, B.K., 2015. Methamphetamine effects on blood-brain barrier structure and function. Front. Neurosci. 9, 69. https://doi.org/10.3389/fnins.2015.00069.
O'Dell, S.J., Weihmuller, F.B., Marshall, J.F., 1991. Multiple methamphetamine injections induce marked increases in extracellular striatal dopamine which correlate with subsequent neurotoxicity. Brain Res. 564, 256–260. https://doi.org/10.1016/0006-8993(91)91461-9.
Okamoto, K., 2014. Organellophagy: eliminating cellular building blocks via selective autophagy. J. Cell Biol. 205, 435–445. https://doi.org/10.1083/jcb.201402054.
Okerlund, N.D., Schneider, K., Leal-Ortiz, S., Montenegro-Venegas, C., Kim, S.A., Garner, L.C., Waites, C.L., Gundelfinger, E.D., Reimer, R.J., Garner, C.C., 2018. Erratum: bassoon controls presynaptic autophagy through Atg5. Neuron 2017 (93), 897–913. https://doi.org/10.1016/j.neuron.2018.01.010 e7, S0896627317300508.
Palikaras, K., Tavernarakis, N., 2020. Regulation and roles of mitophagy at synapses. Mech. Ageing Dev. 187, 111216 https://doi.org/10.1016/j.mad.2020.111216.
Palmisano, N.J., Rosario, N., Wysocki, M., Hong, M., Grant, B., Meléndez, A., 2017. The recycling endosome protein RAB-10 promotes autophagic flux and localization of the transmembrane protein ATG-9. Autophagy 13, 1742–1753. https://doi.org/10.1080/15548627.2017.1356976.
Parra, L.A., Baust, T.B., Smith, A.D., Jaumotte, J.D., Zigmond, M.J., Torres, S., Leak, R.K., Pino, J.A., Torres, G.E., 2016. The molecular chaperone Hsc70 interacts with tyrosine hydroxylase to regulate enzyme activity and synaptic vesicle localization. J. Biol. Chem. 291, 17510–17522. https://doi.org/10.1074/jbc.M116.728782.
Pasquali, L., Busceti, C.L., Fulceri, F., Paparelli, A., Fornai, F., 2010. Intracellular pathways underlying the effects of lithium. Behav. Pharmacol. 21, 473–492. https://doi.org/10.1097/FBP.0b013e32833da5da.
Perreault, M.L., Hasbi, A., Alijaniaram, M., Fan, T., Varghese, G., Fletcher, P.J., Seeman, P., O'Dowd, B.F., George, S.R., 2010. The dopamine D1-D2 receptor heteromer localizes in dynorphin/enkephalin neurons: increased high affinity state following amphetamine and in schizophrenia. J. Biol. Chem. 285, 36625–36634. https://doi.org/10.1074/jbc.M110.159954.
Pietrocola, F., Mariño, G., Lissa, D., Vacchelli, E., Malik, S.A., Niso-Santano, M., Zamzami, N., Galluzzi, L., Maiuri, M.C., Kroemer, G., 2012. Pro-autophagic polyphenols reduce the acetylation of cytoplasmic proteins. Cell Cycle 11, 3851–3860. https://doi.org/10.4161/cc.22027.
Pigulevskiy, I., Lieberman, O.J., Sulzer, D., 2020. Autophagic bias in the striatum. Autophagy 16, 1148–1149. https://doi.org/10.1080/15548627.2020.1743070.
Pitaksalee, R., Sanvarinda, Y., Sinchai, T., Sanvarinda, Pantip, Thampithak, A., Jantaratnotai, N., Jariyawat, S., Tuchinda, P., Govitrapong, P., Sanvarinda, Pimtip, 2015. Autophagy inhibition by caffeine increases toxicity of methamphetamine in SH-SY5Y neuroblastoma cell line. Neurotox. Res. 27, 421–429. https://doi.org/10.1007/s12640-014-9513-9.
Pla, A., Pascual, M., Renau-Piqueras, J., Guerri, C., 2014. TLR4 mediates the impairment of ubiquitin-proteasome and autophagy-lysosome pathways induced by ethanol treatment in brain. Cell Death Dis. 5 https://doi.org/10.1038/cddis.2014.46 e1066–e1066.
Pogorelov, V.M., Nomura, J., Kim, J., Kannan, G., Ayhan, Y., Yang, C., Taniguchi, Y., Abazyan, B., Valentine, H., Krasnova, I.N., Kamiya, A., Cadet, J.L., Wong, D.F., Pletnikov, M.V., 2012. Mutant DISC1 affects methamphetamine-induced sensitization and conditioned place preference: a comorbidity model. Neuropharmacology 62, 1242–1251. https://doi.org/10.1016/j.neuropharm.2011.02.003.
Polajnar, M., Žerovnik, E., 2014. Impaired autophagy: a link between neurodegenerative and neuropsychiatric diseases. J. Cell. Mol. Med. 18, 1705–1711. https://doi.org/10.1111/jcmm.12349.
Polito, V.A., Li, H., Martini-Stoica, H., Wang, B., Yang, L., Xu, Y., Swartzlander, D.B., Palmieri, M., Ronza, A., Lee, V.M., Sardiello, M., Ballabio, A., Zheng, H., 2014. Selective clearance of aberrant tau proteins and rescue of neurotoxicity by transcription factor EB. EMBO Mol. Med. 6, 1142–1160. https://doi.org/10.15252/emmm.201303671.
Puri, D., Subramanyam, D., 2019. Stress – (self) eating: epigenetic regulation of autophagy in response to psychological stress. FEBS J. https://doi.org/10.1111/febs.14826.
Purves-Tyson, T.D., Owens, S.J., Rothmond, D.A., Halliday, G.M., Double, K.L., Stevens, J., McCrossin, T., Shannon Weickert, C., 2017. Putative presynaptic dopamine dysregulation in schizophrenia is supported by molecular evidence from post-mortem human midbrain. Transl. Psychiatry 7, e1003. https://doi.org/10.1038/tp.2016.257.
Qin, Y., Qiu, J., Wang, P., Liu, J., Zhao, Y., Jiang, F., Lou, H., 2020. Impaired autophagy in microglia aggravates dopaminergic neurodegeneration by regulating NLRP3 inflammasome activation in experimental models of Parkinson's disease. Brain Behav. Immun. S0889-1591, 30760–30761. https://doi.org/10.1016/j.bbi.2020.10.010.
Quan, L., Ishikawa, T., Michiue, T., Li, D.R., Zhao, D., Oritani, S., Zhu, B.L., Maeda, H., 2004. Ubiquitin-immunoreactive structures in the midbrain of methamphetamine abusers. Leg. Med. 7, 144–150. https://doi.org/10.1016/j.legalmed.2004.11.002.
Radfar, S.R., Rawson, R.A., 2014. Current research on methamphetamine: epidemiology, medical and psychiatric effects, treatment, and harm reduction efforts. Addict. Health 6, 146–154.
Reichel, C.M., Ramsey, L.A., Schwendt, M., McGinty, J.F., See, R.E., 2012. Methamphetamine-induced changes in the object recognition memory circuit. Neuropharmacology 62, 1119–1126. https://doi.org/10.1016/j.neuropharm.2011.11.003.
Robinson, T.E., Berridge, K.C., 2000. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 95, 91–117. https://doi.org/10.1046/j.1360-0443.95.8s2.19.x.
Robinson, T.E., Berridge, K.C., 2008. Review. The incentive sensitization theory of addiction: some current issues. Philos. Trans. R. Soc. Lond. B Biol. Sci. 363, 3137–3146.
Robison, A.J., Nestler, E.J., 2011. Transcriptional and epigenetic mechanisms of addiction. Nat. Rev. Neurosci. 12, 623–637. https://doi.org/10.1038/nrn3111.
Ruan, Q.T., Yazdani, N., Blum, B.C., Beierle, J.A., Lin, W., Coelho, M.A., Fultz, E.K., Healy, A.F., Shahin, J.R., Kandola, A.K., Luttik, K.P., Zheng, K., Smith, N.J., Cheung, J., Mortazavi, F., Apicco, D.J., Varman, D.R., Ramamoorthy, S., Ash, P.E.A., Rosene, D.L., Emili, A., Wolozin, B., Szumlinski, K.K., Bryant, C.D., 2020. A mutation in hnRNPH1 that decreases methamphetamine-induced reinforcement, reward, and dopamine release and increases synaptosomal hnRNP H and mitochondrial proteins. J. Neurosci. 40, 107–130. https://doi.org/10.1523/JNEUROSCI.1808-19.2019.

Rubinsztein, D.C., Bento, C.F., Deretic, V., 2015. Therapeutic targeting of autophagy in neurodegenerative and infectious diseases. J. Exp. Med. 212, 979–990. https://doi.org/10.1084/jem.20150956.

Rumpf, J.J., Albers, J., Fricke, C., Mueller, W., Classen, J., 2017. Structural abnormality of substantia nigra induced by methamphetamine abuse. Mov. Disord. 32, 1784–1788. https://doi.org/10.1002/mds.27205.

Runwal, G., Stamatakou, E., Siddiqi, F.H., Puri, C., Zhu, Y., Rubinsztein, D.C., 2019. LC3-positive structures are prominent in autophagy-deficient cells. Sci. Rep. 9, 10147. https://doi.org/10.1038/s41598-019-46657-z.

Ryskalin, L., Limanaqi, F., Frati, A., Busceti, C.L., Fornai, F., 2018. mTOR-related brain dysfunctions in neuropsychiatric disorders. Int. J. Mol. Sci. 19, 2226. https://doi.org/10.3390/ijms19082226.

Sahu, R., Kaushik, S., Clement, C.C., Cannizzo, E.S., Scharf, B., Follenzi, A., Potolicchio, I., Nieves, E., Cuervo, A.M., Santambrogio, L., 2011. Microautophagy of cytosolic proteins by late endosomes. Dev. Cell 20, 131–139. https://doi.org/10.1016/j.devcel.2010.12.003.

Sandoval, V., Riddle, E.L., Hanson, G.R., Fleckenstein, A.E., 2002. Methylphenidate redistributes vesicular monoamine transporter-2: role of dopamine receptors. J. Neurosci. 22, 8705–8710. https://doi.org/10.1523/jneurosci.22-19-08705.2002.

Sandoval, V., RIddle, E.L., Hanson, G.R., Fleckenstein, A.E., 2003. Methylphenidate alters vesicular monoamine transport and prevents methamphetamine-induced dopaminergic deficits. J. Pharmacol. Exp. Ther. 304, 1181–1187. https://doi.org/10.1124/jpet.102.045005.

Sato, S., Uchihara, T., Fukuda, T., Noda, S., Kondo, H., Saiki, S., Komatsu, M., Uchiyama, Y., Tanaka, K., Hattori, N., 2018. Loss of autophagy in dopaminergic neurons causes Lewy pathology and motor dysfunction in aged mice. Sci. Rep. 8, 2813. https://doi.org/10.1038/s41598-018-21325-w.

Scheyer, A.F., Loweth, J.A., Christian, D.T., Uejima, J., Rabei, R., Le, T., Dolubizno, H., Stefanik, M.T., Murray, C.H., Sakas, C., Wolf, M.E., 2016. AMPA receptor plasticity in accumbens core contributes to incubation of methamphetamine craving. Biol. Psychiatry 80, 661–670. https://doi.org/10.1016/j.biopsych.2016.04.003.

Schmidt, C.J., Gibb, J.W., 1985. Role of the dopamine uptake carrier in the neurochemical response to methamphetamine: effects of amfonelic acid. Eur. J. Pharmacol. 109, 73–80. https://doi.org/10.1016/0014-2999(85)90541-2.

Schneider, J.L., Miller, A.M., Woesner, M.E., 2016. Autophagy and Schizophrenia: A Closer Look at How Dysregulation of Neuronal Cell Homeostasis Influences the Pathogenesis of Schizophrenia. Einstein J. Biol. Med. 31 (1-2), 34–39. https://doi.org/10.23861/EJBM201631752.

Settembre, C., Zoncu, R., Medina, D.L., Vetrini, F., Erdin, Serkan, Erdin, Serpiluckac, Huynh, T., Ferron, M., Karsenty, G., Vellard, M.C., Facchinetti, V., Sabatini, D.M., Ballabio, A., 2012. A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB. EMBO J. 31, 1095–1108. https://doi.org/10.1038/emboj.2012.32.

Shah, A., Silverstein, P.S., Singh, D.P., Kumar, A., 2012. Involvement of metabotropic glutamate receptor 5, AKT/PI3K Signaling and NF-κB pathway in methamphetamine-mediated increase in IL-6 and IL-8 expression in astrocytes. J. Neuroinflammation 9, 547. https://doi.org/10.1186/1742-2094-9-52.

Shehata, M., Matsumura, H., Okubo-Suzuki, R., Ohkawa, N., Inokuchi, K., 2012. Neuronal stimulation induces autophagy in hippocampal neurons that is involved in AMPA receptor degradation after chemical long-term depression. J. Neurosci. 32, 10413–10422. https://doi.org/10.1523/JNEUROSCI.4533-11.2012.

Shehata, M., Abdou, K., Choko, K., Matsuo, M., Nishizono, H., Inokuchi, K., 2018. Autophagy enhances memory erasure through synaptic destabilization. J. Neurosci. 38, 3809–3822. https://doi.org/10.1523/JNEUROSCI.3505-17.2018.

Shin, E.J., Dang, D.K., Hwang, Y.G., Tran, H.Q., Sharma, N., Jeong, J.H., Jang, C.G., Nah, S.Y., Nabeshima, T., Yoneda, Y., Cadet, J.L., Kim, H.C., 2019. Significance of protein kinase C in the neuropsychotoxicity induced by methamphetamine-like psychostimulants. Neurochem. Int. 124, 162–170. https://doi.org/10.1016/j.neuint.2019.01.014.

Silva, M.C., Nandi, G.A., Tentarelli, S., Gurrell, I.K., Jamier, T., Lucente, D., Dickerson, B. C., Brown, D.G., Brandon, N.J., Haggarty, S.J., 2020. Prolonged tau clearance and stress vulnerability rescue by pharmacological activation of autophagy in tauopathy neurons. Nat. Commun. 11, 3258. https://doi.org/10.1038/s41467-020-16984-1.

Snider, S.E., Vunck, S.A., Van Den Oord, E.J.C.G., Adkins, D.E., McClay, J.L., Beardsley, P.M., 2012. The glial cell modulators, ibudilast and its amino analog, AV1013, attenuate methamphetamine locomotor activity and its sensitization in mice. Eur. J. Pharmacol. 679, 75–80. https://doi.org/10.1016/j.ejphar.2012.01.013.

Sokoloff, P., Diaz, J., Le Foll, B., Guillin, O., Leriche, L., Bezard, E., Gross, C., 2006. The dopamine D3 receptor: a therapeutic target for the treatment of neuropsychiatric disorders. CNS Neurol. Disord. Drug Targets 5 (1), 25–43. https://doi.org/10.2174/187152706784111551.

Solís, O., García-Sanz, P., Martín, A.B., Granado, N., Sanz-Magro, A., Podlesniy, P., Trullas, R., Murer, M.G., Maldonado, R., Moratalla, R., 2019. Behavioral sensitization and cellular responses to psychostimulants are reduced in D2R knockout mice. Addict. Biol. e12840. https://doi.org/10.1111/adb.12840.

Song, J.X., Lu, J.H., Liu, L.F., Chen, L.L., Durairajan, S.S.K., Yue, Z., Zhang, H.Q., Li, M., 2014. HMGB1 is involved in autophagy inhibition caused by SNCA/a-synuclein overexpression :a process modulated by the natural autophagy inducer corynoxine B. Autophagy 10, 144–154. https://doi.org/10.4161/auto.26751.

Song, W.H., Yi, Y.J., Sutovsky, M., Meyers, S., Sutovsky, P., 2016. Autophagy and ubiquitin-proteasome system contribute to sperm mitophagy after mammalian fertilization. Proc. Natl. Acad. Sci. U. S. A. 113, E5261–E5270. https://doi.org/10.1073/pnas.1605844113.

Sonsalla, P.K., Jochnowitz, N.D., Zeevalk, G.D., Oostveen, J.A., Hall, E.D., 1996. Treatment of mice with methamphetamine produces cell loss in the substantia nigra. Brain Res. 738, 172–175. https://doi.org/10.1016/0006-8993(96)00995-X.

Soukup, S.F., Kuenen, S., Vanhauwaert, R., Manetsberger, J., Hernández-Díaz, S., Swerts, J., Schoovaerts, N., Vilain, S., Gounko, N.V., Vints, K., Geens, A., De Strooper, B., Verstreken, P., 2016. A LRRK2-Dependent EndophilinA phosphoswitch is critical for macroautophagy at presynaptic terminals. Neuron 92, 829–844. https://doi.org/10.1016/j.neuron.2016.09.037.

Stenmark, H., 2009. Rab GTPases as coordinators of vesicle traffic. Nat. Rev. Mol. Cell Biol. 10, 513–525. https://doi.org/10.1038/nrm2728.

Stephans, S.E., Yamamoto, B.K., 1995. Effect of repeated methamphetamine administrations on dopamine and glutamate efflux in rat prefrontal cortex. Brain Res. 700, 99–106. https://doi.org/10.1016/0006-8993(95)00938-M.

Subu, R., Jayanthi, S., Cadet, J.L., 2020. Compulsive methamphetamine taking induces autophagic and apoptotic markers in the rat dorsal striatum. Arch. Toxicol. 94 (10), 3515–3526. https://doi.org/10.1007/s00204-020-02844-w. Epub 2020 Jul 16. PMID: 32676729; PMCID: PMC7502530.

Sulzer, D., 2011. How addictive drugs disrupt presynaptic dopamine neurotransmission. Neuron. 69, 628–649. https://doi.org/10.1016/j.neuron.2011.02.010.

Sulzer, D., Rayport, S., 1990. Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: a mechanism of action. Neuron 5, 797–808. https://doi.org/10.1016/0896-6273(90)90339-H.

Sulzer, D., Zecca, L., 1999. Intraneuronal dopamine-quinone synthesis: a review. Neurotox. Res. 1, 181–195. https://doi.org/10.1007/bf03033289.

Sumitomo, A., Yukitake, H., Hirai, K., Horike, K., Ueta, K., Chung, Y., Warabi, E., Yanagawa, T., Kitaoka, S., Furuyashiki, T., Narumiya, S., Hirano, T., Niwa, M., Sibille, E., Hikida, T., Sakurai, T., Ishizuka, K., Sawa, A., Tomoda, T., 2018a. Ulk2 controls cortical excitatory-inhibitory balance via autophagic regulation of p62 and GABAA receptor trafficking in pyramidal neurons. Hum. Mol. Genet. 27, 3165–3176. https://doi.org/10.1093/hmg/ddy219.

Sumitomo, A., Horike, K., Hirai, K., Butcher, N., Boot, E., Sakurai, T., Nucifora Jr., F.C., Bassett, A.S., Sawa, A., Tomoda, T., 2018b. A mouse model of 22q11.2 deletions: molecular and behavioral signatures of Parkinson's disease and schizophrenia. Sci. Adv. 4, eaar6637. https://doi.org/10.1126/sciadv.aar6637.

Sun, L., Lian, Y., Ding, J., Meng, Y., Li, C., Chen, L., Qiu, P., 2019. The role of chaperone-mediated autophagy in neurotoxicity induced by alpha-synuclein after methamphetamine exposure. Brain Behav. 9, e01352 https://doi.org/10.1002/brb3.1352.

Surmeier, D.J., Shen, W., Day, M., Gertler, T., Chan, S., Tian, X., Plotkin, J.L., 2010. The role of dopamine in modulating the structure and function of striatal circuits. Prog. Brain Res. 183, 148–167. https://doi.org/10.1016/S0079-6123(10)83008-0.

Suzuki, O., Hattori, H., Asano, M., Oya, M., Katsumata, Y., 1980. Inhibition of monoamine oxidase by d-methamphetamine. Biochem. Pharmacol. 29, 2071–2073. https://doi.org/10.1016/0006-2952(80)90493-1.

Szatmári, Z., Kis, V., Lippai, M., Hegedus, K., Faragó, T., Lorincz, P., Tanaka, T., Juhász, G., Sass, M., 2014. Rab11 facilitates cross-talk between autophagy and endosomal pathway through regulation of Hook localization. Mol. Biol. Cell 25, 522–531. https://doi.org/10.1091/mbc.E13-10-0574.

Taguchi, K., Fujikawa, N., Komatsu, M., Ishii, T., Unno, M., Akaike, T., Motohashi, H., Yamamoto, M., 2012. Keap1 degradation by autophagy for the maintenance of redox homeostasis. Proc. Natl. Acad. Sci. U. S. A. 109, 13561–13566. https://doi.org/10.1073/pnas.1121572109.

Tallóczy, Z., Martinez, J., Joset, D., Ray, Y., Gácser, A., Toussi, S., Mizushima, N., Nosanchuk, J., Goldstein, H., Loike, J., Sulzer, D., Santambrogio, L., 2008. Methamphetamine inhibits antigen processing, presentation, and phagocytosis. PLoS Pathog. 4, e28. https://doi.org/10.1371/journal.ppat.0040028.

Tang, F.L., Erion, J.R., Tian, Y., Liu, W., Yin, D.M., Ye, J., Tang, B., Mei, L., Xiong, W.C., 2015. VPS35 in dopamine neurons is required for endosome-to- golgi retrieval of Lamp2a, a receptor of chaperone- mediated autophagy that is critical for α-synuclein degradation and prevention of pathogenesis of Parkinson's disease. J. Neurosci. 35, 10613–10628. https://doi.org/10.1523/JNEUROSCI.0042-15.2015.

Taylor, T.N., Alter, S.P., Wang, M., Goldstein, D.S., Miller, G.W., 2014. Reduced vesicular storage of catecholamines causes progressive degeneration in the locus ceruleus. Neuropharmacology. 76, 97–105. https://doi.org/10.1016/j.neuropharm.2013.08.033.

Tehrani, A.M., Boroujeni, M.E., Aliaghaei, A., Feizi, M.A.H., Safaralizadeh, R., 2019. Methamphetamine induces neurotoxicity-associated pathways and stereological changes in prefrontal cortex. Neurosci. Lett. 712, 134478 https://doi.org/10.1016/j.neulet.2019.134478.

Thomas, D.M., Francescutti-Verbeem, D.M., Kuhn, D.M., 2008. The newly synthesized pool of dopamine determines the severity of methamphetamine-induced neurotoxicity. J. Neurochem. 105, 605–616. https://doi.org/10.1111/j.1471-4159.2007.05155.x.

Tian, Y., Tang, F.L., Sun, X.D., Wen, L., Mei, L., Tang, B.S., Xiong, W.C., 2015. VPS35-deficiency results in an impaired AMPA receptor trafficking and decreased dendritic spine maturation. Mol. Brain 8, 70. https://doi.org/10.1186/s13041-015-0156-4.

Toker, L., Agam, G., 2015. Mitochondrial dysfunction in psychiatric morbidity: current evidence and therapeutic prospects. Neuropsychiatr. Dis. Treat. 11, 2441–2447. https://doi.org/10.2147/NDT.S70346.

Tomoda, T., Yang, K., Sawa, A., 2020. Neuronal autophagy in synaptic functions and psychiatric disorders. Biol. Psychiatry 87, 787–796. https://doi.org/10.1016/j.biopsych.2019.07.018.

Tooze, S.A., Schiavo, G., 2008. Liaisons dangereuses: autophagy, neuronal survival and neurodegeneration. Curr. Opin. Neurobiol. 18, 504–515. https://doi.org/10.1016/j.conb.2008.09.015.

Tulloch, I., Afanador, L., Mexhitaj, I., Ghazaryan, N., GarzaGongora, A.G., Angulo, J.A., 2011. A single high dose of methamphetamine induces apoptotic and necrotic striatal cell loss lasting up to 3 months in mice. Neuroscience 193, 162–169. https://doi.org/10.1016/j.neuroscience.2011.07.020.

Uehara, T., Sumiyoshi, T., Itoh, H., Kurachi, M., 2004. Inhibition of dopamine synthesis with alpha-methyl-p-tyrosine abolishes the enhancement of methamphetamine-induced extracellular dopamine levels in the amygdala of rats with excitotoxic lesions of the entorhinal cortex. Neurosci. Lett. 356, 21–24. https://doi.org/10.1016/j.neulet.2003.11.018.

Ugun-Klusek, A., Tatham, M.H., Elkharaz, J., Constantin-Teodosiu, D., Lawler, K., Mohamed, H., Paine, S.M.L., Anderson, G., John Mayer, R., Lowe, J., Ellen Billett, E., Bedford, L., 2017. Continued 26S proteasome dysfunction in mouse brain cortical neurons impairs autophagy and the Keap1-Nrf2 oxidative defence pathway. Cell Death Dis. 8, e2531. https://doi.org/10.1038/cddis.2016.443.

Uytterhoeven, V., Lauwers, E., Maes, I., Miskiewicz, K., Melo, M.N., Swerts, J., Kuenen, S., Wittocx, R., Corthout, N., Marrink, S.J., Munck, S., Verstreken, P., 2015. Hsc70-4 deforms membranes to promote synaptic protein turnover by endosomal microautophagy. Neuron 88, 735–748. https://doi.org/10.1016/j.neuron.2015.10.012.

Valvassori, S., Cararo, J., Peper-Nascimento, J., Ferreira, C., Gava, F., Dal-Pont, G., Andersen, Quevedo, J., 2020. Protein kinase C isoforms as a target for manic-like behaviors and oxidative stress in a dopaminergic animal model of mania. Prog. Neuro-Psychopharmacology Biol. Psychiatry 101, 109940. https://doi.org/10.1016/j.pnpbp.2020.109940.

Vanan, S., Zeng, X., Yoong Chia, S., Jiang, M., Zhang, K., Ting Saw, W., Padmanabhan Lee Kong, P., Yu, W.-P.A., Zhi-Dong Zhou, S., Tan, E.-K., Zeng, L., 2020. Altered striatal dopamine levels in Parkinson's disease VPS35 D620N mutant transgenic aged mice. Mol. Brain 13, 164. https://doi.org/10.21203/rs.3.rs-51781/v2.

Vanderwerf, S.M., Buck, D.C., Wilmarth, P.A., Sears, L.M., David, L.L., Morton, D.B., Neve, K.A., 2015. Role for Rab10 in methamphetamine-induced behavior. PLoS One 10, e0136167. https://doi.org/10.1371/journal.pone.0136167.

Vartak, R.S., Rodin, A., Oddo, S., 2019. Differential activation of the mTOR/autophagy pathway predicts cognitive performance in APP/PS1 mice. Neurobiol. Aging 83, 105–113. https://doi.org/10.1016/j.neurobiolaging.2019.08.018.

Velásquez-Martinez, M.C., Vázquez-Torres, R., Jiménez-Rivera, C.A., 2012. Activation of alpha1-adrenoceptors enhances glutamate release onto ventral tegmental area dopamine cells. Neuroscience 216, 18–30. https://doi.org/10.1016/j.neuroscience.2012.03.056.

Vijayan, V., Verstreken, P., 2017. Autophagy in the presynaptic compartment in health and disease. J. Cell Biol. 216, 1895–1906. https://doi.org/10.1083/jcb.201611113.

Volkow, N.D., 2009. Substance use disorders in Schizophrenia - Clinical implications of comorbidity. Schizophr. Bull. 35, 469–472. https://doi.org/10.1093/schbul/sbp016.

Volkow, N.D., Morales, M., 2015. The brain on drugs: from reward to addiction. Cell. 162, 712–725. https://doi.org/10.1016/j.cell.2015.07.046.

Volkow, N.D., Chang, L., Wang, G.J., Fowler, J.S., Ding, Y.S., Sedler, M., Logan, J., Franceschi, D., Gatley, J., Hitzemann, R., Gifford, A., Wong, C., Pappas, N., 2001. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am. J. Psychiatry 158, 2015–2021. https://doi.org/10.1176/appi.ajp.158.12.2015.

Volkow, N.D., Fowler, J.S., Wang, G.J., Shumay, E., Telang, F., Thanos, P.K., Alexoff, D., 2010a. Distribution and pharmacokinetics of methamphetamine in the human body: clinical implications. PLoS One 5, e15269. https://doi.org/10.1371/journal.pone.0015269.

Volkow, N.D., Wang, G.J., Fowler, J.S., Tomasi, D., Telang, F., Baler, R., 2010b. Addiction: decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. BioEssays. 32, 748–755. https://doi.org/10.1002/bies.201000042.

Volz, T.J., Fleckenstein, A.E., Hanson, G.R., 2007. Methamphetamine-induced alterations in monoamine transport: implications for neurotoxicity, neuroprotection and treatment. Addiction 102, 44–48. https://doi.org/10.1111/j.1360-0443.2007.01771.x.

Wagner, G.C., Ricaurte, G.A., Seiden, L.S., Schuster, C.R., Miller, R.J., Westley, J., 1980. Long-lasting depletions of striatal dopamine and loss of dopamine uptake sites following repeated administration of methamphetamine. Brain Res. 181, 151–160. https://doi.org/10.1016/0006-8993(80)91265-2.

Wang, J.Da, Cao, Y.L., Li, Q., Yang, Y.P., Jin, M., Chen, D., Wang, F., Wang, G.H., Qin, Z. H., Hu, L.F., Liu, C.F., 2015. A pivotal role of FOS-mediated BECN1/Beclin 1 upregulation in dopamine D2 and D3 receptor agonist-induced autophagy activation. Autophagy 11, 2057–2073. https://doi.org/10.1080/15548627.2015.1100930.

Wang, C., Niu, M., Zhou, Z., Zheng, X., Zhang, L., Tian, Y., Yu, X., Bu, G., Xu, H., Ma, Q., Zhang, Ywu, 2016. VPS35 regulates cell surface recycling and signaling of dopamine receptor D1. Neurobiol. Aging 46, 22–31. https://doi.org/10.1016/j.neurobiolaging.2016.05.016.

Wang, D., Ji, X., Liu, J., Li, Z., Zhang, X., 2018. Dopamine receptor subtypes differentially regulate autophagy. Int. J. Mol. Sci. 19, 1540. https://doi.org/10.3390/ijms19051540.

Wei, Z.B., Yuan, Y.F., Jaouen, F., Ma, M.S., Hao, C.J., Zhang, Z., Chen, Q., Yuan, Z., Yu, L., Beurrier, C., Li, W., 2016. SLC35D3 increases autophagic activity in midbrain dopaminergic neurons by enhancing BECN1-ATG14-PIK3C3 complex formation. Autophagy 12, 1168–1179. https://doi.org/10.1080/15548627.2016.1179402.

Weidenauer, A., Bauer, M., Sauerzopf, U., Bartova, L., Praschak-Rieder, N., Sitte, H.H., Kasper, S., Willeit, M., 2017. Making sense of: sensitization in schizophrenia. Int. J. Neuropsychopharmacol. 20, 1–10. https://doi.org/10.1093/ijnp/pyw081.

Weikel, K.A., Cacicedo, J.M., Ruderman, N.B., Ido, Y., 2016. Knockdown of GSK3β increases basal autophagy and AMPK signalling in nutrient-laden human aortic endothelial cells. Biosci. Rep. 36, 382. https://doi.org/10.1042/BSR20160174.

Weinshenker, D., Schroeder, J.P., 2007. There and back again: a tale of norepinephrine and drug addiction. Neuropsychopharmacology 32, 1433–1451. https://doi.org/10.1038/sj.npp.1301263.

Weinshenker, D., Ferrucci, M., Busceti, C.L., Biagioni, F., Lazzeri, G., Liles, L.C., Lenzi, P., Pasquali, L., Murri, L., Paparelli, A., Fornai, F., 2008. Genetic or pharmacological blockade of noradrenaline synthesis enhances the neurochemical, behavioral, and neurotoxic effects of methamphetamine. J. Neurochem. 105, 471–483. https://doi.org/10.1111/j.1471-4159.2007.05145.x.

Wen, L., Tang, F.L., Hong, Y., Luo, S.W., Wang, C.L., He, W., Shen, C., Jung, J.U., Xiong, F., Lee, Dhoon, Zhang, Q.G., Brann, D., Kim, T.W., Yan, R., Mei, L., Xiong, W. C., 2011. VPS35 haploinsufficiency increases Alzheimer's disease neuropathology. J. Cell Biol. 195, 765–779. https://doi.org/10.1083/jcb.201105109.

Wersinger, C., Chen, J., Sidhu, A., 2004. Bimodal induction of dopamine-mediated striatal neurotoxicity is mediated through both activation of D1 dopamine receptors and autoxidation. Mol. Cell. Neurosci. 25, 124–137. https://doi.org/10.1016/j.mcn.2003.10.002.

Wilson, J.M., Levey, A.I., Rajput, A., Ang, L., Guttman, M., Shannak, K., Niznik, H.B., Hornykiewicz, O., Pifl, C., Kish, S.J., 1996. Differential changes in neurochemical markers of striatal dopamine nerve terminals in idiopathic Parkinson's disease. Neurology 47, 718–726. https://doi.org/10.1212/wnl.47.3.718.

Wu, C.W., Ping, Y.H., Yen, J.C., Chang, C.Y., Wang, S.F., Yeh, C.L., Chi, C.W., Lee, H.C., 2007. Enhanced oxidative stress and aberrant mitochondrial biogenesis in human neuroblastoma SH-SY5Y cells during methamphetamine induced apoptosis. Toxicol. Appl. Pharmacol. 220, 243–251. https://doi.org/10.1016/j.taap.2007.01.011.

Wu, Q., Xu, H., Wang, W., Chang, F., Jiang, Y., Liu, Y., 2016. Retrograde trafficking of VMAT2 and its role in protein stability in non-neuronal cells. J. Biomed. Res. 30, 502–509. https://doi.org/10.7555/JBR.30.20160061.

Wu, S., Fagan, R.R., Uttamapinant, C., Lifshitz, L.M., Fogarty, K.E., Ting, A.Y., Melikian, H.E., 2017. The dopamine transporter recycles via a retromer-dependent postendocytic mechanism: tracking studies using a novel fluorophore-coupling approach. J. Neurosci. 37, 9438–9452. https://doi.org/10.1523/JNEUROSCI.3885-16.2017.

Xiao, Q., Yan, P., Ma, X., Liu, H., Perez, R., Zhu, A., Gonzales, E., Tripoli, D.L., Czerniewski, L., Ballabio, A., Cirrito, J.R., Diwan, A., Lee, J.M., 2015. Neuronal-targeted TFEB accelerates lysosomal degradation of app, reducing Aβ generation and amyloid plaque pathogenesis. J. Neurosci. 35, 12137–12151. https://doi.org/10.1523/JNEUROSCI.0705-15.2015.

Xie, Z., Klionsky, D.J., 2007. Autophagosome formation: core machinery and adaptations. Nat. Cell Biol. 9, 1102–1109. https://doi.org/10.1038/ncb1007-1102.

Xie, X.L., He, J.T., Wang, Z.T., Xiao, H.Q., Zhou, W.T., Du, S.H., Xue, Y., Wang, Q., 2018. Lactulose attenuates METH-induced neurotoxicity by alleviating the impaired autophagy, stabilizing the perturbed antioxidant system and suppressing apoptosis in rat striatum. Toxicol. Lett. 289, 107–113. https://doi.org/10.1016/j.toxlet.2018.03.015.

Xilouri, M., Brekk, O.R., Stefanis, L., 2016. Autophagy and Alpha-Synuclein: relevance to parkinson's disease and related synucleopathies. Mov. Disord. 31, 178–192. https://doi.org/10.1002/mds.26477.

Xu, C.M., Wang, J., Wu, P., Xue, Y.X., Zhu, W.L., Li, Q.Q., Zhai, H.F., Shi, J., Lu, L., 2011. Glycogen synthase kinase 3β in the nucleus accumbens core is critical for methamphetamine-induced behavioral sensitization. J. Neurochem. 118, 126–139. https://doi.org/10.1111/j.1471-4159.2011.07281.x.

Yabe, I., Yaguchi, H., Kato, Y., Miki, Y., Takahashi, H., Tanikawa, S., Shirai, S., Takahashi, I., Kimura, M., Hama, Y., Matsushima, M., Fujioka, S., Kano, T., Watanabe, M., Nakagawa, S., Kunieda, Y., Ikeda, Y., Hasegawa, M., Nishihara, H., Ohtsuka, T., Tanaka, S., Tsuboi, Y., Hatakeyama, S., Wakabayashi, K., Sasaki, H., 2018. Mutations in bassoon in individuals with familial and sporadic progressive supranuclear palsy-like syndrome. Sci. Rep. 8, 819. https://doi.org/10.1038/s41598-018-19198-0.

Yan, P., Xu, D., Ji, Y., Yin, F., Cui, J., Su, R., Wang, Y., Zhu, Y., Wei, S., Lai, J., 2019. LiCl pretreatment ameliorates adolescent methamphetamine exposure-induced long-term alterations in behavior and hippocampal ultrastructure in adulthood in mice. Int. J. Neuropsychopharmacol. 22, 303–316. https://doi.org/10.1093/ijnp/pyz001.

Yang, K., Wei, M., Yang, Z., Fu, Z., Xu, R., Cheng, C., Chen, X., Chen, S., Dammer, E., Le, W., 2020a. Activation of dopamine receptor D1 inhibits glioblastoma tumorigenicity by regulating autophagic activity. Cell. Oncol. https://doi.org/10.1007/s13402-020-00550-4. Online ahead of print.

Yang, Y., Karsli-Uzunbas, G., Poillet-Perez, L., Sawant, A., Hu, Z.S., Zhao, Y., Moore, D., Hu, W., White, E., 2020b. Autophagy promotes mammalian survival by suppressing oxidative stress and p53. Genes Dev. 34, 688–700. https://doi.org/10.1101/gad.335570.119.

Yu, L., Chen, Y., Tooze, S.A., 2018. Autophagy pathway: cellular and molecular mechanisms. Autophagy. 14, 207–215. https://doi.org/10.1080/15548627.2017.1378838.

Zavodszky, E., Seaman, M.N.J., Moreau, K., Jimenez-Sanchez, M., Breusegem, S.Y., Harbour, M.E., Rubinsztein, D.C., 2014. Mutation in VPS35 associated with Parkinson's disease impairs WASH complex association and inhibits autophagy. Nat. Commun. 5, 3828. https://doi.org/10.1038/ncomms4828.

Zhang, M., Schekman, R., 2013. Unconventional secretion, unconventional solutions. Science 340, 559–561. https://doi.org/10.1126/science.1234740.

Zhang, X., Lee, T.H., Xiong, X., Chen, Q., Davidson, C., Wetsel, W.C., Ellinwood, E.H., 2006. Methamphetamine induces long-term changes in GABAA receptor α2 subunit and GAD67 expression. Biochem. Biophys. Res. Commun. 351, 300–305. https://doi.org/10.1016/j.bbrc.2006.10.046.

Zhang, L., Yu, J., Pan, H., Hu, P., Hao, Y., Cai, W., Zhu, H., Yu, A.D., Xie, X., Ma, D., Yuan, J., 2007. Small molecule regulators of autophagy identified by an image-based high-throughput screen. Proc. Natl. Acad. Sci. U. S. A. 104, 19023–19028. https://doi.org/10.1073/pnas.0709695104.

Zhang, D., Isack, N.R., Glodowski, D.R., Liu, J., Chen, C.C.H., Shawn Xu, X.Z., Grant, B. D., Rongo, C., 2012. RAB-6.2 and the retromer regulate glutamate receptor recycling through a retrograde pathway. J. Cell Biol. 196, 85–101. https://doi.org/10.1083/jcb.201104141.

Zhang, S., Hu, L., Jiang, J., Li, H., Wu, Q., Ooi, K., Wang, J., Feng, Y., Zhu, D., Xia, C., 2020. HMGB1/RAGE axis mediates stress-induced RVLM neuroinflammation in mice via impairing mitophagy flux in microglia. J. Neuroinflammation 17, 15. https://doi.org/10.1186/s12974-019-1673-3.

Zhao, J., Zhai, B., Gygi, S.P., Goldberg, A.L., 2015. MTOR inhibition activates overall protein degradation by the ubiquitin proteasome system as well as by autophagy. Proc. Natl. Acad. Sci. U. S. A. 112, 15790–15797. https://doi.org/10.1073/pnas.1521919112.

Zhou, J., Tan, S.H., Nicolas, V., Bauvy, C., Yang, N.Di, Zhang, J., Xue, Y., Codogno, P., Shen, H.M., 2013a. Activation of lysosomal function in the course of autophagy via mTORC1 suppression and autophagosome-lysosome fusion. Cell Res. 23, 508–523. https://doi.org/10.1038/cr.2013.11.

Zhou, M., Li, W., Huang, S., Song, J., Kim, J.Y., Tian, X., Kang, E., Sano, Y., Liu, C., Balaji, J., Wu, S., Zhou, Yu, Zhou, Ying, Parivash, S.N., Ehninger, D., He, L., Song, H., Ming, Gli, Silva, A.J., 2013b. MTOR inhibition ameliorates cognitive and affective deficits caused by Disc1 knockdown in adult-born dentate granule neurons. Neuron 77, 647–654. https://doi.org/10.1016/j.neuron.2012.12.033.

Zhu, J.P.Q., Xu, W., Angulo, J.A., 2006a. Methamphetamine-induced cell death: selective vulnerability in neuronal subpopulations of the striatum in mice. Neuroscience 140, 607–622. https://doi.org/10.1016/j.neuroscience.2006.02.055.

Zhu, J.P.Q., Xu, W., Angulo, N., Angulo, J.A., 2006b. Methamphetamine-induced striatal apoptosis in the mouse brain: comparison of a binge to an acute bolus drug administration. Neurotoxicology 27, 131–136. https://doi.org/10.1016/j.neuro.2005.05.014.

Zhu, J., Chen, Y., Zhao, N., Cao, G., Dang, Y., Han, W., Xu, M., Chen, T., 2012. Distinct roles of dopamine D3 receptors in modulating methamphetamine-induced behavioral sensitization and ultrastructural plasticity in the shell of the nucleus accumbens. J. Neurosci. Res. 90, 895–904. https://doi.org/10.1002/jnr.22821.

Zoncu, R., Efeyan, A., Sabatini, D.M., 2011. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat. Rev. Mol. Cell Biol. 12, 21–35. https://doi.org/10.1038/nrm3025.

Zweben, J.E., Cohen, J.B., Christian, D., Galloway, G.P., Salinardi, M., Parent, D., Iguchi, M., 2004. Methamphetamine Treatment Project. Psychiatric symptoms in methamphetamine users. Am. J. Addict. 13, 181–190.