EDITORIAL

Themed Section: Monoamines

Updating Neuropathology and Neuropharmacology of Monoaminergic systems

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Due to the great progress and development of modern technology, our understanding of neuropsychiatric disorders biological, physiological, and metabolic processes has advanced tremendously. However, we still face many challenges in drug discovery and development targeting because neuropsychiatric disorders have a complex etiology with multiple points of possible intervention. This is also apparent in consideration of the plurality of targets that bind antipsychotics, anti-Parkinsonian, or antidepressant drugs, indicating the need to develop multi-target compounds for a polypharmacological approach (Hopkins, 2008).

Understanding the interactions of neurotransmission systems especially among monoamines is an important step for the optimization of therapeutic strategies for many if not all of these neuropsychiatric disorders. Neurotransmitters such as dopamine, serotonin, noradrenaline or histamine play a central role in the pathophysiology of major neuropsychiatric illnesses, including anxiety and mood disorders, schizophrenia, autism-spectrum disorders, Parkinson's disease, epilepsy, and dementias (De Deurwaerdère & Di Giovanni, 2016; Simic et al., 2016; Venzi et al., 2016). Numerous medicines targeting monoaminergic systems have been used successfully but most require adjustments due to the emergence of side effects. However, the efficacy of these medicines stress that the strategy to correct abnormal signalling of monoaminergic neurotransmitters is appropriate. A further complication arises in that monoaminergic systems establish close relationships with other neurotransmitter systems (Chesselet, 1984), so it is likely that a pharmacological action toward one system will more or less directly affect the other one. This is highlighted by well-known associations such as the 5-HT/DA interaction (De Deurwaerdère & Di Giovanni, 2016; Di Giovanni *et al.*, 2008; Di Matteo *et al.*, 2008),

the glutamate/DA interaction (Carlsson & Carlsson, 1990), and the 5-HT/GABA interaction (Crunelli & Di Giovanni, 2014; Soubrie, 1986). Moreover, neurotransmitter-binding proteins such as receptors, transporters and common metabolic enzymes have commonalities in their binding sites that must be considered as the starting points for development of new tools to diagnose and drugs to treat specific clusters of symptoms.

The European Cooperation in Science and Technology (COST, Figure 1) Action CM1103 "Structure-based drug design for diagnosis and treatment of neurological diseases: dissecting and modulating complex function in the monoaminergic systems of the brain" is a good example of the advances possible through interdisciplinary collaboration on these difficult problems (see http://www.cost.eu/COST_Actions/cmst/CM1103). During the four year life of the Action, different European laboratories using innovative computational approaches contributed to the analysis of the pharmocophores, identified novel hits, and verified the suitability of new compounds against multiple targets. New series of compounds were synthesized and assessed experimentally against the design targets for Alzheimer's disease (AD) such as monoamine oxidases (MAO) and cholinesterases (ChE), then promising leads examined for other beneficial properties such as anti-oxidant activity and promoting cell survival. Compounds addressing new combinations of targets have also been developed. At the organism level, compounds have also been examined in animal models of epilepsy and vascular dementia, and linked to human data by members involved in translational research (see (De Deurwaerdere *et al.*, 2016; Ramsay & De Deurwaerdere, 2014; Ramsay & Di Giovanni, 2014). The articles contributed here present some of insights gained during

the collaborative research and other contributions from researchers working in this field.

Figure 1. European Cooperation in Science and Technology. COST is a pan-European intergovernmental framework. Its mission is to enable break-through scientific and technological developments leading to new concepts and products and thereby contribute to strengthening Europe's research and innovation capacities. It allows researchers, engineers and scholars to jointly develop their own ideas and take new initiatives across all fields of science and technology, while promoting multi- and interdisciplinary approaches.

The purpose of this special issue is to collect relevant research and review papers covering the wide spectrum of the neuropathology and neuropharmacology of monoaminergic systems. Guiard and colleagues (Zemdegs *et al.*, 2016) report on the bidirectional link between type 2 diabetes mellitus (T2DM) and depression. These metabolic and mental disorders are major public concerns since each pathology affects 350 millions people worldwide and have terrific economic impact. Although growing evidence support that T2DM may cause depression, some important issues have yet to be clarified. In particular, the neurobiological mechanisms by which T2DM negatively reverberates on mood and to what extent it might influence the therapeutic outcome of serotonergic antidepressant drugs are two crucial questions

that were addressed in this study. In agreement with epidemiological data, the authors demonstrated that increased body weight, hyperglycaemia and impaired glucose tolerance were correlated with anxiogenic-/depressive-like symptoms in mice fed with a high-fat diet., They also emphasize (for the first time in this animal model of comorbid T2DM/depression) that such behavioural abnormalities were associated with decreased extracellular 5-HT levels in the hippocampus resulting from increased sensitivity of the dorsal raphe 5-HT$_{1A}$ autoreceptor. Moreover, the beneficial effect of prolonged administration of escitalopram was abolished in mice fed a high fat diet. On the contrary, withdrawal of the high fat diet completely reversed the metabolic impairments and positively changed symptoms of anxiety, although some behavioural anomalies persisted. In a context of increasing prescription of antidepressant medication (Mojtabai & Olfson, 2014), understanding and predicting response to specific treatment could have benefits not only as regards the economic burden related to depression but also for the patients. This study shed some light on the fact that stabilizing metabolic parameter would be a prerequisite before expecting beneficial effects of antidepressant drugs, notably SSRIs, in the comorbidity of T2DM and depression. This hypothesis paves the way for clinical investigations that might help identifying the most adequate therapeutic strategy.

Two contributions from Bortolato and colleagues (Godar *et al.*, 2015) are studies focused on dopamine and its receptors in the regulation of prepulse inhibition (PPI) of the acoustic startle, a well-known cross-species index of sensorimotor gating, typically impaired in several neuropsychiatric disorders featuring dopaminergic imbalances, such as Tourette syndrome (TS), schizophrenia and mania. D1CT-7 mice, one of the best-characterized animal models of TS, exhibit PPI deficits in response to short-term spatial confinement (SC). These D1CT-7 mice are characterized by a

neuropotentiating transgene in select populations of neurons containing D1 dopamine receptors, and exhibit specific tic-like responses. A mild environmental stressor also produced a significant exacerbation in tic-like responses, in a fashion sensitive to benchmark therapies for TS. Taken together, their data highlight a novel experimental platform to study the neurobiological links between environmental stress and TS manifestations (including tic-like responses) in animal models. The second study (Mosher *et al.*, 2015) showed that hooded Long-Evans rats display PPI deficits in response to the selective activation of both D1 and D2 dopamine receptors. Conversely, only D2 agonists have PPI-disrupting properties in Sprague-Dawley and Wistar albino rats. One of the first-documented examples of D1 sensitivity in PPI in rats, this model may prove valuable to study the involvement of the D1 receptor in rat models of TS, schizophrenia and mania.

Moving more to studies where the interactions of the neurotransmission systems are relevant to degeneration, De Deurwaerdère and Ugedo (Miguelez *et al.*, 2016) focused on the effect of the L-DOPA, the gold standard medication of Parkinson's disease, on serotonergic system. L-DOPA therapeutic superiority compared to other medication is impaired by numerous side-effects including dyskinesia. Agonists at 5-HT_{1A} receptors can reduce L-DOPA-induced dyskinesia but these compounds have their own side-effects (Carta *et al.*, 2007). Indirectly, the selective serotonin reuptake inhibitors could stimulate 5-HT_{1A} receptors but their efficacy could be lowered due to the own effects of L-DOPA on serotonergic neuron activity (Navailles *et al.*, 2011). Here, Miguelez et al. (2016) studied the acute and long-term L-DOPA effects and the activity of dorsal raphe serotonergic neurons in 6-OHDA-lesioned rats, a preclinical model of Parkinson's disease. They found that the 5-HT_{1A} receptor-dependent control of serotonergic neurons is unaltered in dyskinetic rats and that the SSRI fluoxetine

loses its efficacy to inhibit the 5-HT$_{1A}$ receptor-dependent inhibitory control of serotonergic neurons in the presence of L-DOPA. This study raises caution to the use of SSRI in the treatment of depression or dyskinesia in L-DOPA-treated Parkinsonian patients (Miguelez *et al.*, 2016)

Also relevant to dyskinesia in Parkinson's disease, is a review (García *et al.*, 2016) of the evidence on cannabinoid–dopamine interactions emphasising the function of the basal ganglia and the control of movement. Dopaminergic neurons do not contain CB1 receptors but these receptors are located on neurons present in regions innervated by dopaminergic neurons, which allows relevant bidirectional interactions. However, additional direct mechanisms may also facilitate these interactions, for example, through TRPV1 and CB2 receptors located in dopaminergic neurons as well as through postsynaptic interactions of CB1 receptors with D1/D2 receptors. It is possible that cannabinoids might have therapeutic potential through these actions that can facilitate a normalization of dopaminergic transmission in states such as Parkinson's disease.

Ponimaskin and Kondaurova and their colleagues (Kulikova et al., 2016) propose an original work focusing on 5-HT$_{1A}$ receptors. The role played by presynaptic and postsynaptic 5-HT$_{1A}$ receptors in the action of antidyskinetic, antipsychotic, antidepressant or anxiolytic drugs is one of the main lines of research regarding serotonin-based medicines (De Deurwaerdère and Di Giovanni, 2016). Genetic predisposition regarding pre- and postsynaptic 5-HT$_{1A}$ receptor responses could condition distinct pharmacological responses and appropriate preclinical models are needed. The authors (Kulikova et al., 2016) created two mouse lines, B6-M76C and B6-M76B, by transfer of a chromosomic locus selected from CBA mice to C57BL/6

genetic background. This locus, which predisposes CBA mice to catalepsy, contains 5-HT$_{1A}$ receptor gene. They analysed the pharmacological, biochemical, cellular and behavioural properties in the two lines. The genetic transfer to the C57Bl6 led to decreased pre-synaptic and increased post-synaptic functional responses of the 5-HT$_{1A}$ receptor. This feature makes the Bl6-M76C mouse an attractive model for the pharmacological screening of 5-HT$_{1A}$ receptor-related drugs specifically acting either on the pre- or post-synaptic receptors.

The final article looks beyond the neurotransmitter systems to other factors affecting neuronal survival in the face of ageing and neurodegenerative diseases. Youdim and colleagues (Weinreb *et al.*, 2015) reviewed the neuroprotective effects of hybrid agents targeting MAOs, cholinesterases, iron load, and β-amyloid accumulation in ageing and AD. Nowadays, AD is accepted as a complex neurodegenerative disorder with multifaceted cerebral pathologies and it is widely accepted that an effective therapy for AD could result from the use of multifunctional drugs affecting more than one target involved in the disease pathology. The potential benefits of novel multimodal neuroprotective, brain-permeable drugs, recently developed by Youdim and collaborators, are a valuable therapeutic approach for AD treatment.

The key message from these studies is the cross-talk between systems. Fundamental research to identify key proteins that influence the functional pathways is essential for future multi-target drug design. In turn, multi-target compounds will aid the dissection of the complex pathways in neuropharmacology and our understanding of how the brain works and how best to normalise its function.

Acknowledgments

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