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PERSPECTIVE

AT1 Receptor as a Potential Target in Amphetamine-induced Neuroinflammation

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1. NEUROINFLAMMATION

The central nervous system (CNS) under normal conditions is immunologically inactive; since the immune cells from the periphery are unable to cross the blood-brain barrier. However, the immunity mechanisms and their mediated responses (generated by both CNS immunity system and the peripheral immunity mechanisms) are important for CNS recovery after infection or acute injury. In contrast, chronic inflammatory and autoimmune responses strongly contribute to pathological states. Shreds of evidence suggest that the deregulated CNS innate immunity is a key factor in the initiation and progression of several neurological disorders. In this sense, neuroinflammation, which is a complex innate immune response of neural tissue that restrains infection, eliminates pathogen cell debris and mis-folded proteins. Although, in chronic neurological disorders, persistent neuroinflammation results detrimental to neural tissue. The characteristics of neuroinflammation rely on the glial cells´ interaction and the resulting response [1]. Glial cells are the most abundant and widely distributed cells in the CNS and they interact with neurons and blood vessels. The cellular and molecular mechanisms of glial cells in neuroinflammation remain poorly understood due to their complexity. To this respect, neuroinflammation is a highly variable response depending on inflammatory signals (Glial cells play distinct roles under different scenarios). In addition, similar to immune cells, glial cells play "double-faced" roles in the processes of neuroinflammation, depending on the course of the disease and certain environments of inflammation. Moreover, the outcomes of neuroinflammation result from joint actions of multiple glial cell types and peripheral immune cells [2].

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A growing body of evidence suggests that neuroinflammation is commonly associated with several neurologic disorders, and its attenuation brings beneficial effects. Several psychoactive drugs are known to induce neuroinflammation associated with neuronal dysfunction and cognitive deficits.

2. AMPHETAMINES EFFECTS AND NEUROINFLAMMATION

The structural amphetamines' homology with catecholamine neurotransmitters allows it to act as a false substrate for dopamine transporter proteins (DAT) at a presynaptic level. They disrupt catecholamine uptake, inducing an extensive increase of noradrenaline and dopamine in the synaptic terminal. Moreover, amphetamines induce dopamine release, increasing the cytosolic monoamine level by inhibiting the vesicular monoamine transporter and monoamine oxidase activity.

Amphetamines constitute a group of drugs associated with clinical use and illicit consumption. D-Amphetamine (AMPH) is the simplest compound that presents all chemical properties underlying their physiological actions. In rodents, AMPH is commonly used as a pharmacological tool to promote dopamine imbalance, and this neuroadaptation - including cellular, molecular, and metabolic modifications- takes place along with neuroinflammation. The particular AMPH effects make it a useful tool in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. However, there is a high risk of misuse and abuse. In this respect, AMPH and methamphetamine (METH) are the major contributors to the global burden of disease attributable to drug use disorders after opioids (United Nations Office on Drugs and Crime 2017). In this sense, the illegal market reached 29 million users in the last two decades, which comprise 0.6% of the global population aged between 15 to 64 (United Nations Office on Drugs and Crime 2019). Moreover, according to United Nations Office on Drugs and Crime 2019, AMPH and METH confiscations have doubled and quintupled, respectively, including more than 240 tons worldwide between 2009-2017.

METH has a greater ability to induce dopamine release, despite AMPH´s higher affinity to the DAT. METH has

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lipophilic properties that facilitate its diffusion and entrance to presynaptic endings, besides its DAT-dependent uptake. METH and AMPH exert different effects on mitochondrial and monoamino oxidase levels [3]. Most of the available studies are focused on METH's neurotoxic and neuroinflammatory effects since its potency is higher than AMPH. However, the abuse risk and action similarity between these psychostimulants give AMPH the potential to recreate the observed METH alterations. Moreover, it has been found that METH and AMPH were equipotent to induce neurodegeneration in the striatum and parietal cortex of rats [4]. Indeed, AMPH induces dopaminergic nerve ending degeneration in nonhuman primates, even at therapeutic doses, to treat ADHD in humans [5].

Amphetamines' neurotoxicity occurs as a consequence of numerous mechanisms in which oxidative stress and excitotoxicity play an important role [6]. Oxidative stress results from an excess of free radical formation, mainly radical oxygen species and reactive nitrogen species. Moreover, an increased glutamate release promotes excitotoxic damage.

The neurotransmitter receptors present in microglial cells sense neurotransmission imbalance, and dopamine receptors are among them [7]. Dopamine is the main neurotransmitter system involved in amphetamines effects, and it is not surprising that exposure to these psychostimulants induces changes in microglial function leading to neuroinflammation. Indeed, microgliosis was observed in several brain regions of METH users [8]. Moreover, AMPH exposure in rodents induces specific brain regional patrons of microglial activation. In this respect, brain areas where dopaminergic neuron bodies are present, like the substantia nigra and ventral tegmental, showed low sensitivity to amphetamines. In contrast, brain areas with dopaminergic endings showed to be more vulnerable [9]. Accordingly, microglial activation is more common in limbic areas such as the striatum, hippocampus, amygdala, and cortex. Moreover, different regional sensitivity patterns have been described along with different species. In mice, the hippocampus and striatum are frequently altered. In contrast, rats show little change in these areas, while the thalamus and parietal cortex are usually altered [9].

3. ANGIOTENSIN II AT_1 RECEPTOR

Two principal subtypes of angiotensin II (Ang II) receptors named AT_1 and AT_2 were initially described. The characterization was made based on their affinity to specific ligands and later by molecular cloning. The AT_1 receptor (AT_1-R) is a typical heptahelical G-protein –coupled receptor made up of 359 amino acids with a molecular weight of 41,000 [10]. AT_1-R stimulation is involved in multiple cellular responses, mainly through Gq/11 coupling, stimulates phospholipases A2, C, and D, and activates inositol trisphosphate/Ca^{2+} signalling, protein quinase C isoforms, and MAPKs, as well as several tyrosine kinases (Pyk2, Src, Tyks, Fak) scaffold proteins (G protein-coupled receptor kinase-interacting protein 1, p130Cas, paxillin, vinculin) receptor tyrosine kynases, and the nuclear factor-κB pathway. The AT_1-R acts *via* G12/13 proteins and Gi/o in rodents and activates G protein-independent signalling pathways, such as β arrestin-mediated MAPK activation and the Jak/STAT [11, 12]. The AT_1-R is present in neurons, astrocytes, microglia, and endothelial cells and mediates most of the known biological effects of Ang II [13, 14]. Regarding AT_1-R associated pathological role, alterations in homo or heterodimerization seem to be involved. However, several deleterious actions of AT_1-R are initiated by locally generated Ang II rather than circulating [12].

4. BRAIN ANGIOTENSIN II AT_1 RECEPTOR AND NEUROINFLAMMATION

Brain angiotensin II acts as a pleiotropic system through AT_1-R activation. In pathological conditions, the AT_1-R expressed in astrocytes, microglia, and brain endothelial cells emerges as a key mediator in the development of an oxidative/inflammatory microenvironment and glial activation. Ang II is a well-known proinflammatory factor in peripheral tissues, sharing signal transduction pathways with other inflammatory stimuli, and the anti-inflammatory effects of AT_1-R antagonists (ARB) have been established for hypertension and diabetes [15]. Using an experimental model of inflammation (Lipopolysaccharide, LPS), it was found that ARB administration decreases the excessive production of proinflammatory cytokines and their release into the circulation. Moreover, ARB treatment also decreased the production of cytokines and microglia activation in the brain cortex [15]. It is known that the inflammatory cascade in the brain is followed by activation of microglia, the central resident immune cells, with induction of additional inflammatory cascades and results, if not controlled, in glial and neuronal damage. In the same line, ARBs have been reported to prevent dopaminergic neuronal death during brain inflammation [16]. Particularly, AT_1-R promotes the initiation and progression of local brain inflammatory and oxidative responses under dopamine imbalance conditions, as described in animal models of senescence [17] and Parkinson's disease [18].

5. ANGIOTENSIN II MODULATES AMPHETAMINE-INDUCED GLIAL RESPONSES *VIA* AT_1 RECEPTOR

Our group obtained evidence that strongly support the involvement of AT_1-R in the development of AMPH-induced neuroadaptation at neurochemical, structural, and behavioral levels [19-21]. Reciprocally, AMPH exposure induces long-lasting overexpression of functional AT_1-R in dopamine-innervated areas [21] and brain microvessels [22]. However, AT_1-R functionality was altered by AMPH since intracerebral angiotensin II-elicited classical responses were modified [23].

Repeated AMPH administration induced an endurable increase in astrocyte and microglial markers expression, concomitant with apoptosis in the prefrontal and somatosensory cortex. Glial reactivity, observed as increased glial marker expression, has long been recognized as a specific marker for AMPH toxicity [24]. It has been proposed that the main detrimental effects of amphetamines could be the result of a transient increase in dopaminergic and glutamatergic neurotransmission. Moreover, AMPH's deleterious effects extend to the microvascular rearrangement in the prefrontal and somatosensory cortex, supporting their region-specific toxicity. It is important to highlight that vascular network modifications are known to

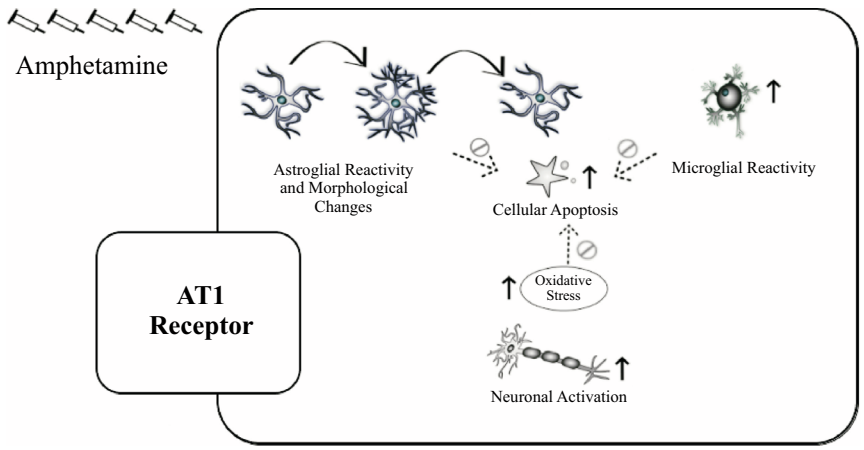

Figure 1. Schematic representation showing the principal events associated with amphetamine-induced neuroinflammation and AT_1-R blockade protective role. Amphetamine-induced cellular apoptosis, altered astrocytes and microglia functionality, and oxidative stress due to neuronal over activation and dopamine toxicity. AT_1-R blockade blunted the deleterious effects of amphetamine acting at different levels. The punctuated line indicates the possible mechanisms under AT_1-R modulation.

be closely related to inflammatory processes [22]. Regarding this last, AT_1-R showed to be involved in the development of AMPH-induced alterations in the prefrontal and somatosensory cortex as its blockade prevented the increase in glial marker expression and vascular rearrangement [22, 25, 26]. The role of AT_1-R in the alterations induced by AMPH could be attributed to its multiple actions that include dopamine neurotransmission modulation [27], dopaminergic neurons degeneration by oxidative stress, astrocyte and microglial reactivity, and angiogenesis [28-30]. Particularly, in neuroinflammation associated with dopamine imbalance, Ang II is considered a key mediator in triggering glial cell activation and inflammatory process progression [31]. In the same direction, the protective effects of AT_1-R blockade have been reported for the alterations of dopamine neurotransmission and toxicity induced by methamphetamine [27]. Since the main long-lasting effect of AMPH exposure is dopamine neurotransmission imbalance, prefrontal cortex regional susceptibility could be triggered by its greater dopaminergic innervation. Behavioral tests that evaluate exploration are indicative of prefrontal cortex functional integrity since catecholamine neurotransmission is implicated in the coordination and integration of cues. AMPH-induced working memory and attention deficit in rodents have been related to morphological and structural changes in glial cells in the prefrontal cortex [22, 25]. Thus, cortical hypo-perfusion, glial reactivity, inflammation, and oxidative stress have been related to neuropsychiatric impairments in psychostimulant users, such as attention or decision making deficits. The prefrontal cortex dysfunction described long after AMPH exposure is characterized by cortical hyporeactivity due to decreased glutamate and dopamine levels together with diminished neuronal activity. The proposed phenomenon is in accordance with the data obtained from AMPH users that show improved attentional performance after low doses of AMPH since it induces catecholamine release. Interestingly, AT_1-R blockade prevents working memory and attention deficits induced by AMPH, as well as its inflammatory effects in the prefrontal cortex [22, 25].

CONCLUSION

The above-described evidence prompts us to suggest AT_1-R as a key player in neuroinflammatory events associated with amphetamines (Figure **1**). Interestingly, ARBs are currently used in clinics with a low incidence of side effects. The data presented aim to encourage the focus on ARBs as an alternative pharmacological tool in amphetamine associated disorders.

AUTHORS' CONTRIBUTIONS

CRJ, LB, and CB wrote and revised the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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