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The Effects of Locus Coeruleus and Norepinephrine in Methamphetamine Toxicity

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Abstract: The activity of locus coeruleus (LC) neurons has been extensively investigated in a variety of behavioural states. In fact this norepinephrine (NE)-containing nucleus modulates many physiological and pathological conditions including the sleep-waking cycle, movement disorders, mood alterations, convulsive seizures, and the effects of drugs such as psychostimulants and opioids. This review focuses on the modulation exerted by central NE pathways on the behavioural and neurotoxic effects produced by the psychostimulant methamphetamine, essentially the modulation of the activity of mesencephalic dopamine (DA) neurons. In fact, although NE in itself mediates some behavioural effects induced by methamphetamine, NE modulation of DA release is pivotal for methamphetamine-induced behavioural states and neurotoxicity. These interactions are discussed on the basis of the state of the art of the functional neuroanatomy of central NE- and DA systems. Emphasis is given to those brain sites possessing a remarkable overlapping of both neurotransmitters.

Keywords: Behaviour, Dopamine, Locus Coeruleus, Methamphetamine, Neurochemistry, Norepinephrine, Substantia Nigra, Drugs of Abuse.

1. THE CHEMICAL NEUROANATOMY OF NE-CONTAINING LC NEURONS

The main source of NE in the brain is represented by an NE pontine nucleus, which corresponds to the nucleus Locus Coeruleus (LC, A6, according to the original catecholamine nuclei classification by Dahlstrom and Fuxe [1]). This is located in the upper part of the floor of the fourth ventricle. This nucleus is highly preserved phylogenically [2-4]. Rather than being a single brain nucleus, LC represents a nuclear complex, which is located bilaterally within the lateral pontine central grey, and includes scattered catecholamine neurons close to the brachium conjunctivum, and within the central tegmental regions of the pontine gray matter [5, 6].

Caudal NE neurons are separated from the LC complex and are located in the medullary ventrolateral reticular formation (A1 and A2 areas, according to the description by Dahlstrom and Fuxe, [1]). They send their axons to restricted target areas and play an important role in regulating autonomic functions and neuroendocrine control [7].

The LC complex is shaped like a tube, and its major cell types are medium-sized neurons, bearing coarse particles of melanin granules to the cytoplasm [8]. In young adult human the LC complex contains approximately 60,000 neurons, which decrease down to 40,000 during normal ageing [9, 10]. Most NE neurons are scattered in the LC complex, while one third are packed within the main pontine LC nucleus [11]. In keeping with neuronal density, the dorso-medial compartment of LC contains densely packed neurons, while in the ventrolateral compartment neurons are dispersed [5].

In humans, the rostrocaudal extension of the LC nuclear complex is approximately 16 mm [3, 12]. The rostral end of LC reaches decussation of the trochlear nerve up to the periacqueductal gray of the mesencephalon, while the caudal end descends to the level of the facial nerve [5].

The cytology of LC neurons features both medium- and small-sized neurons, 35-45 μm and 15-25 μm diameter respectively. The medium-sized neurons are multipolar cells generally round in shape, with only a few dendrites located in the rostral part of the nucleus and often extending into surrounding structures. The small spindly LC neurons have two tufts of dendrites and are found within the ventral LC complex [5].

LC axons branch profusely, thus allowing a single NE axon to send terminals throughout the entire cerebral cortex. Nearly all levels of the CNS are thus innervated by LC axons, which provide the sole NE innervation of the isocortex, allocortex, and cerebellar cortex [5, 6, 13-17], while they caudally innervate the medulla, and spinal cord [3, 18].

The multiple divergence of axon collaterals is concomitant with the occurrence of diffuse non synaptic effects on neighbouring cells. This leads to a widespread

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release of NE from the LC axons which may reach a variety of targets. NE thus acts as a neuromodulator within a circumscribed microenvironment, rather than as a classic neurotransmitter [19, 20]. In fact, NE activity extends beyond neurons and involves astrocytes and cerebral blood vessels. In line with this, NE system also plays a fundamental role in the physiology of the blood-brain barrier and in glial cells activity [21, 22]. This includes NE effects on the microglial release of specific cytokines [23, 24]. The paracrine effects of the central NE system due to the marked divergence of axon collaterals is further sustained by the fine morphology of these nerve endings. In fact, NE axon collaterals possess "boutons en passage", consisting of varicosities, rather than classic "boutons terminaux" that are typical of non-monoamine axon terminals. The spikes travelling along the fibre are thus able to release NE from multiple serial sites rather than just from the fibre end.

Interestingly, varicosities along LC axons differ from those described along NE axons arising from other NE nuclei. In fact, while NE axons that arise from LC possess small (0.5 μm) beaded varicosities, axons arising from the medullary A1 and A2 NE cell groups have varicosities with a larger diameter (1±3 μm).

Such a fine anatomical discrepancy has important pathological consequences. In fact, monoamine axons with smaller beaded varicosities have a lower threshold to various neurotoxic insults and are more prone to neurodegeneration compared with the ones bearing large varicosities [25-27]. These considerations call for more in-depth studies aimed at relating the cell biology of synaptic varicosities with selective neuronal vulnerability occurring during neurotoxic insults and neurodegenerative disorders.

2. ANATOMICAL CONNECTIONS OF LC NE NEURONS (FIG. 1)

The classic histofluorescence method of Falck *et al.*, [28] led to the identification of two main ascending pathways from the LC. These were confirmed by immuno-histochemical methods and consist of: 1) a dorsal pathway [29], innervating the entire cerebral cortex, especially motor and premotor areas, the olfactory tubercle, the septum, the bed nucleus of the stria terminalis, the hippocampal formation, and the amygdala [30, 31]; and 2) a ventral or intermediate pathway innervating the hypothalamus, overlapping with NE projections coming from the A1 and A2 regions. Groups of fibers have been described that project from the LC to the subthalamic nucleus [32], substantia nigra (SN, A9 according to Dahlstrom and Fuxe, [1]) [33], and ventral tegmental area (VTA, A10) [34]. Finally, other afferent fibers pass *via* the superior cerebellar peduncle to the cerebellum [35], and a caudal projection has been traced to the reticular formation and the cord as well [36]. The striatum just has a small amount of NE, receiving only scattered fibers from the LC. Nonetheless, these striatal afferents seem to possess a high turnover rate [25, 26, 37].

The main afferents to the LC include projections from the prefrontal cortex (PFC), lateral hypothalamus [38], cerebellum [39], raphe nuclei [40], and amygdala [41]. Furthermore, the LC receives NE afferents from lower medullary A1 and A2 regions [42-44]. In addition, LC receives DA afferents from VTA [45]. In line with the specific aim of the review, below is a brief summary on specific sites for NE-DA interaction.

Morphological analysis indicates that the ventral striatum receives direct NE innervation from the LC at the level of the caudal part of nucleus accumbens (NAc) shell [46, 47]. These NE axons also originate from A2 [48]. On the other hand, the rostral part of the NAc as well as the dorsal striatum have scattered NE innervations [46-48]. These data were recently confirmed by direct catecholamine assay, in situ voltammetry, stimulations of the median forebrain bundle and various pharmacological manipulations [49]. The origin of these fibers is only partly attributed to LC, although this issue remains under debate [25].

3. THE ANATOMY OF NE-DA INTERACTIONS

The interactions between NE and DA have been subject to intense investigation in the neuroanatomy of catecholamine systems, which appear to be reciprocally connected. In fact, LC receives DA afferents from VTA [45] and there is strong evidence for the presence of detectable NE levels in the VTA which derives from multiple sources [50-52]. In fact, two decades ago it was shown that stimulation of VTA neurons increases the activity of the LC [45]. Similarly, A1, and A2 NE nuclei were shown to provide excitatory stimulation to VTA DA neurons [53, 54]. Further indirect evidence for NE-DA interaction at the level of the VTA has been provided by autoradiographic and immunohistochemical studies, showing alpha1 and alpha2-adrenergic receptor (AR) expression in most DA neurons of the VTA [55, 56].

However, the precise source of NE terminals in the VTA was only recently defined in detail [57]. The authors of [58] described the sources of NE in the VTA, SN and retrorubral field (A8). By using retrograde tracing, they showed that NE afferents to the VTA originate mainly from the LC and, to a lesser extent, from A5 (NE neurons placed in the ventrolateral pons); each LC innervates both homo- and contra-lateral VTAs, to a similar extent. Liprando *et al.*, [58] described the interaction between NE terminals and VTA DA neurons by using an immune-electron microscopy dual labeling approach both in rats and monkeys. They showed that the vast majority (more than 70%) of interactions between NE transporter (NET)-positive (i.e. NE-containing) terminals and DA neurons occur between NE varicosities and DA dendrites showing ultrastructural features typical of extra-synaptic sites. This thus confirmed once again that NE fibers have a neuromodulatory extra-synaptic effect on their targets [58].

Among mesocortical DA target areas, PFC is densely innervated by LC-originating NE terminals. Knowledge of the functional effects of this innervation added further details to the "functional anatomy" of LC-PFC interactions. For instance, Hertel *et al.*, [59] showed that alpha2 AR antagonists increase basal DA output in the medial prefrontal cortex through a direct effect on DA terminals within PFC [59].

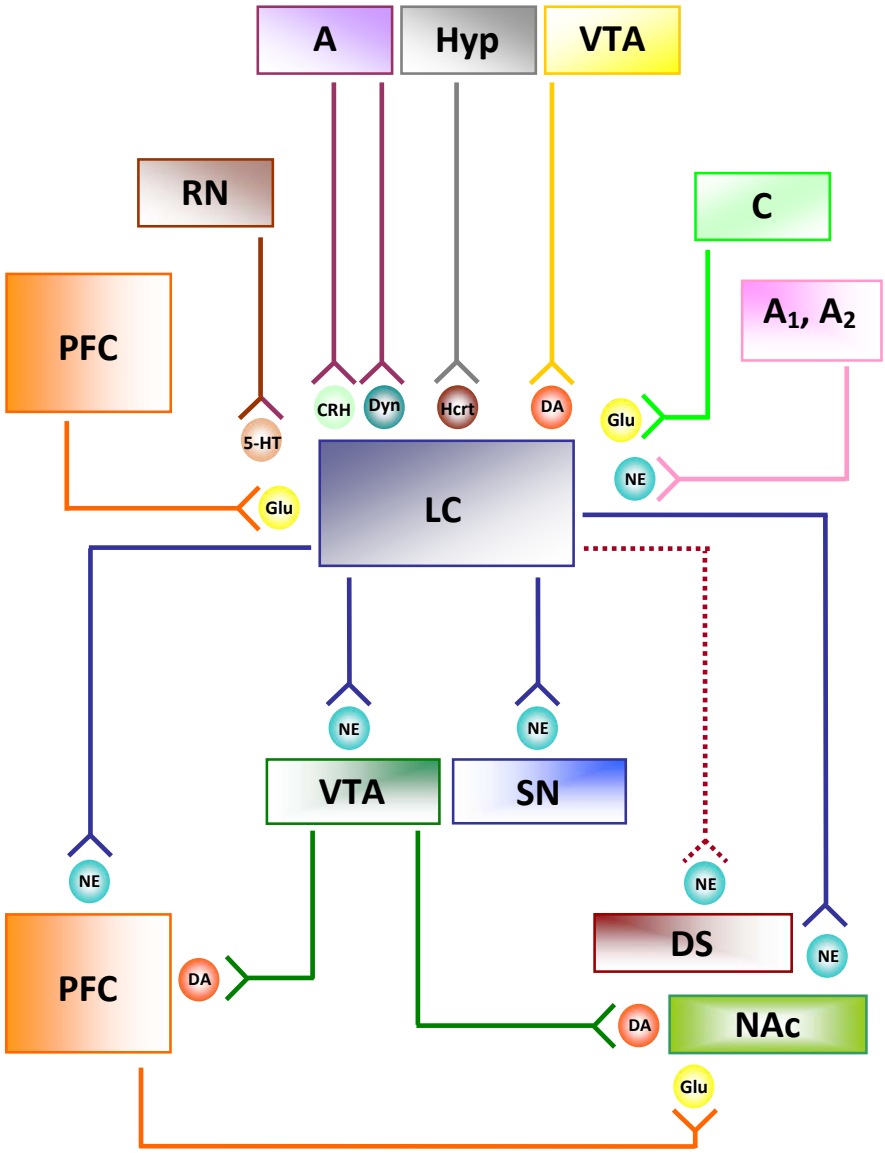

Fig. (1). Locus coeruleus projections to brain areas responsible for amphetamines-induced behavioural responses. Amphetamines cause a massive NE release in all the brain areas that receive NE inputs from locus coeruleus. Locus coeruleus inputs into NAc are suggested by much experimental evidence (see text). An increase in NE-mediated signals on NAc and PFC produces the typical behavioural responses induced by amphetamine derivatives. Conversely, dorsal striatum possesses only scattered NE afferents from locus coeruleus. Locus Coeruleus receives inputs from several cortical and subcortical regions. Descending fibers from cortical areas mainly derive from the dorsolateral and dorsomedial prefrontal cortex. Amigdalo-coeruleus projections releasing corticotropin-releasing hormone and dynorphin suggest the involvement of LC in the control of limbic functions. Hypocretin/orexin innervation from the posterior hypothalamus is involved in the LC regulation of sleep/arousal responses. Finally, monoaminergic innervation to LC derives from raphe nuclei, lower medullary A1 and A2 NE nuclei, and VTA. A, amigdala; A1, A2, NE nuclei; C, cerebellum; CRT, corticotropin-releasing hormone; DA, dopamine; DS, dorsal striatum; Glu, glutamate; Hcrt, hypocretin; Hyp, hypothalamus; 5-HT, serotonin; NAc, nucleus accumbens; NE, norepinephrine; LC, locus coeruleus; PFC, prefrontal cortex; RN, raphe nuclei; SN, substantia nigra; VTA, ventral tegmental area.

Concerning the nigrostriatal system, SN receives direct NE projections from LC, in addition to A1 and A2 nuclei [57].

While anatomical evidence remains unclear, the presence of NE in the dorsal striatum is widely established, as well as high NE turnover, as witnessed by the high ratio between 3-methoxy4-hydroxyphenylglycol (a major metabolite of NE) and NE in the striatum itself (see for instance [25, 26, 60]). This might explain why damage to LC decreases striatal DA release [25, 26, 61-65]. The anatomical connections between LC NE neurons and DA areas is critical to understanding the behavioural effects induced by methamphetamine (METH). In fact, the role of DA in mediating the action of METH changes dramatically depending on the activity of the LC-NE system.

In order to dissect this multi-faceted issue in Section 4 we summarize the molecular events produced by METH on

DA and NE containing cells in order to explain the behavioural effects.

4. MOLECULAR EFFECTS OF METHAMPHETAMINE (METH) ON CATECHOLAMINE (DA AND NE) CELLS

Methamphetamine acts on multiple classes of neurons as well as different molecular targets. In fact a variety of neurotransmitters are released under METH administration - namely, serotonin [66] glutamate [67-69] and acetylcholine [70, 71]. Among these, catecholamine neurons are considered as the main target since METH is a powerful DA and NE releaser [72, 73]. As a consequence, repetitive administration of METH leads to DA-and NE-dependent behavioural sensitization, which can be reproduced in different species.

How METH acts is quite specific and involves three main targets. Briefly, METH produces (i) a disruption to

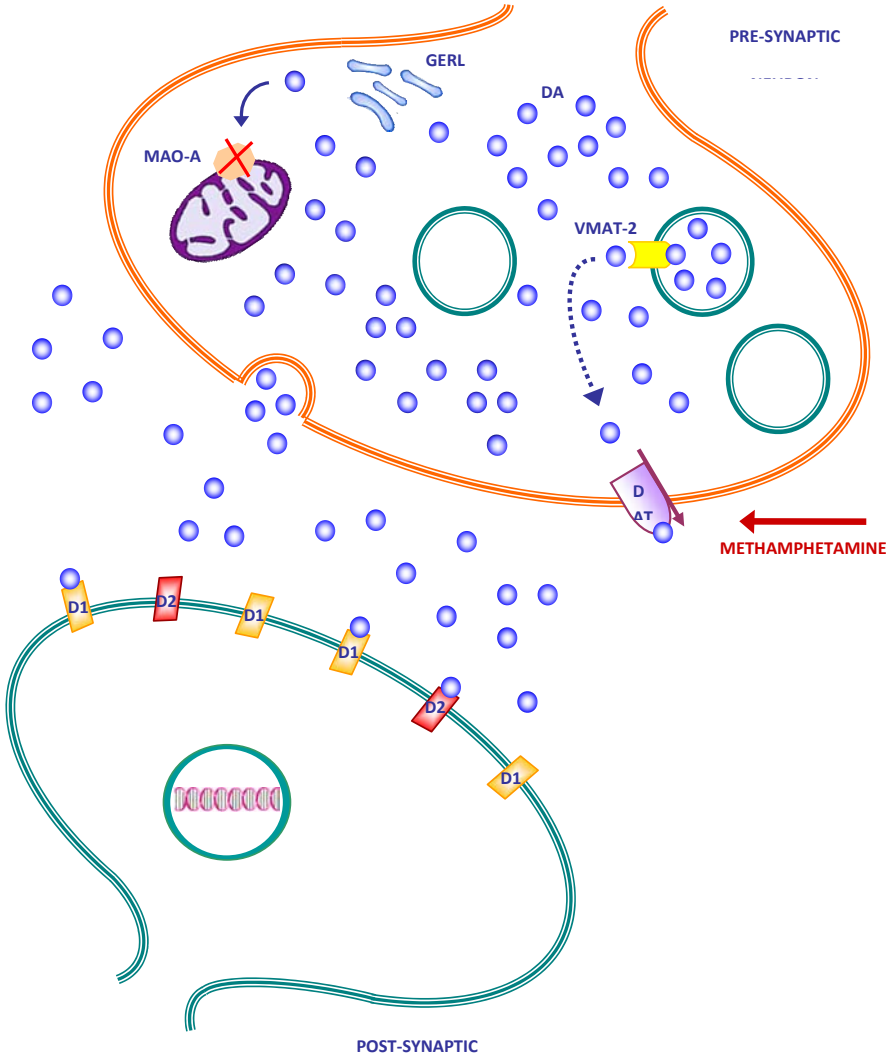

Fig. (2). Neurochemical targets of methamphetamine. The picture shows the biochemical effects of amphetamine derivatives within a DA nerve terminal: 1) the vesicular monoamine transporter (VMAT) type 2, which is responsible for the storage of DA within the synaptic vesicles; 2) the DA transporter (DAT), which takes up DA from the synaptic cleft to the DA axons; 3) the MAO-A, which is responsible for oxidative deamination of DA. Methamphetamine impairs the activity of these proteins at several levels: 1) by reverting the direction of DA transport of both VMAT-2 and DAT; 2) by myslocating VMAT-2 from synaptic vesicles to other membrane systems (i.e. GERL); 3) by inhibiting the activity of the MAO-A. This results in a massive efflux of DA first into the nerve terminal and then into extracellular space. Free DA autoxidates and produces highly reactive intermediate species which are responsible for the oxidative alteration of several proteins and lipids (for a review see [97]). Similar molecular targets can be identified in NE nerve terminals. Methamphetamine has a 10-fold higher affinity for the NE transporter (NET) than DAT. In fact, the same dose of methamphetamine produces an NE release higher than the DA release [72]. This effect might explain the association between NE release and behavioural effects induced by methamphetamine. The effects produced by extracellular DA are thought to be mediated by the activation of both D1-like and D2-like receptors. The former are believed to be critical for the DA component of methamphetamine-induced behavioural sensitization [97]. D1, dopamine receptor type-1; D2, dopamine receptor type-2; DAT, dopamine transporter; GERL, Golgi apparatus, endoplasmic reticulum and lysosomal system; MAO-A, monoamine oxidase type-A; VMAT-2, vesicular monoamine transporter type-2.

physiological DA and NE vesicular storage, by interfering with the vesicular monoamine transporter type-2 (VMAT-2), (ii) it impairs the membrane DA transporter (DAT) [74] and NET [75], (iii) it competitively inhibits intracellular DA and NE metabolism by monoamine oxidase (MAO)-A [76] which are placed within both DA and NE terminals [77] (Fig. **2**).

METH acts on synaptic vesicles in several ways. It:

1) produces an altered proton gradient through the DA/NE storing vesicles, which makes DA readily diffusible from the vesicle to the cytoplasm [78].

2) directly inhibits the VMAT-2 [79, 80], which prevents DA and NE from entering the vesicles.

3) promotes DA and NE efflux from the vesicles to the cytoplasm [81];

4) moves and misplaces VMAT-2 from vesicles to non-physiological compartments, making the vesicles unable to store catecholamines [82, 83], leading to a "bizarre" release which is not related to physiological sites [84].

The effects of METH on catecholamine-storing vesicles produce massive amounts of free cytosolic DA and NE. This plays a key role in both the behavioural and neurotoxic effects of METH intake/administration. The increase in cytosolic DA and NE is accompanied by additional effects which transport massive levels of DA and NE from cytosol to the extracellular space. In fact, large amount of cytosolic catecholamines pass the plasma membrane either by passive diffusion or through a pathological reversion of the transporter [74, 85, 86]. Massive extracellular levels are enhanced by the concomitant inhibition of DA and NE metabolism and uptake (inhibition of MAO, and inhibition of DAT and NET, respectively). Inhibition of metabolism is due to the inhibitory effects of METH on MAO enzymes. Both MAO subtypes are involved, although the effects on MAO-A, which are present within DA and NE terminals, are predominant, while MAO-B are mainly placed in the glial cells [77, 87-92].

In DA terminals, DA is metabolized by MAO-A to the aldehyde 3,4-dihydroxyphenylacetaldehyde (DOPALD), which is rapidly converted by further oxidation to the acid 3,4-dihydroxyphenylacetic acid (DOPAC). On the other hand, in NE terminals the aldehyde produced by MAO-A from NE is preferentially reduced to the corresponding alcohol (which is in fact a glycol, 3,4-dihydroxyphenylethyleneglycol, DOPEG). This slight difference might impact on neuro-toxicity since DOPALD is much more toxic than DOPEG. In spite of that, the effects of METH can be assumed the same when considering intracellular NE and DA since the selective and powerful inhibition of MAO-A is presumed to alter similarly the oxidative deamination of both DA and NE within pre-synaptic terminals. On the other hand, the Ki for NET is 10 fold lower than the Ki for DAT, which leads to 10 fold higher effects of METH on NE compared with DA uptake blockade [72].

Such a difference in the uptake mechanism in the presence of similar MAO inhibition is expected to produce higher extracellular NE compared with DA levels, as demonstrated by seminal papers [72]. This is critical in brain areas such as the PFC in which the numbers of DA and NE terminals are comparable. In this case, NE may have a leading role in sustaining the behavioural effects produced by METH administration [72]. This also occurs partly in the ventral striatum and specific limbic regions, which are rich in both DA and NE axon terminals [67, 93-96].

Turning now to the dorsal striatum, the critical effects of METH are almost exclusively produced on DA terminals and thereby on DA levels. In fact, striatal DA terminals are far in excess compared with NE terminals (roughly 100:1, [25]). The increase in striatal extracellular DA levels goes along with greater diffusion properties to extra-synaptic sites since the uptake (which limits diffusion) is strongly inhibited. Thus, METH produces a striatal scenario featuring a high amount of extracellular DA which spread over a greater distance for a prolonged amount of time. This leads to high and persistent "peaks" in DA levels, which are reminiscent of what occurs during L-DOPA administration in advanced stages of Parkinson's disease [97].

5. METHAMPHETAMINE-INDUCED BEHAVIOURAL EFFECTS

Methamphetamine is known to profoundly affect behavior in humans and in a variety of animal species [98]. Behavioural effects on animals reflect those seen in humans, and are dose-dependent. Low doses of amphetamines increase locomotor activity, such as exploratory behaviour with rearing and sniffing.

Higher or repeated doses switch motor activity from locomotion to repetitive "in place" movements such as automatisms and stereotypies (licking, biting, gnawing). The higher the dose of amphetamines, the earlier the behavioural switch from hyperlocomotion to stereotypies. Moreover, the time spent in stereotypies increases with the dose of amphetamines (these points were extensively reviewed by Seiden *et al.,* [98]). There is thus a different pattern of behavioural effects when METH is administered repeatedly. These behavioural changes mainly consist of exaggerated motor response to moderate doses of METH and above all depend on changes in the receptor signalling at a post-synaptic level.

These effects are produced both directly by NE and *via* modulating the massive DA release. The role of NE emerged in the last decade adding to well-established evidence showing that METH-induced behavioural changes are predominantly due to a robust DA release. In fact, selective damage to DA terminals in the dorsal striatum by 6-hydroxydopamine (6-OHDA) decreases stereotypies and increases locomotor activity induced by amphetamines [99-101], whereas selective damage to DA terminals within the nucleus accumbens (NAc) decreases hyper-locomotion [102]. This suggests that DA in NAc mediates hyperlocomotion, whereas DA in the dorsal striatum mediates stereotypies. In fact selective injections of amphetamine within the NAc [103] as well as in the ventrolateral striatum [104] induce hyper-locomotion, whereas injections in the dorsal striatum produce stereotypies [104-106].

Robust DA release is thus important to produce those behavioural effects occurring immediately after METH intake (acute behavioural effects) and long-term behavioural changes which reflect persistent alterations in some brain areas after repeated exposure to METH (behavioural sensitization).

6. THE ROLE OF NE IN METHAMPHETAMINE-INDUCED BEHAVIOURAL CHANGES

The possibility that NE might be involved in the behavioural effects of psychostimulants was first hypothesized in the early 1960s [107, 108]. This was then supported by studies which found that LC and the dorsal NE bundle are targets of self-stimulation [109-111]. This self-stimulation takes place with a higher threshold in the presence of amphetamines [108, 112, 113]. These results led to the idea that NE mediates some effects of psychostimulants on intracerebral stimulation.

A number of subsequent studies did not confirm this role of NE [113-115]. Thus, starting in the 1970s, DA, rather than NE, was generally accepted as the brain's primary "reward neurotransmitter". However, later studies demonstrated a dissociation between DA release and behavioural responses to amphetamines.

We will thus now look at the effects played by of LC NE on METH-induced behavioural changes. The effects of METH interacting with NE can be divided into direct effects produced by NE and indirect effects due to the influence of NE on DA system

6.1. The Role of NE *per se*

In this context, it needs to be remarked that NE is massively released following METH administration, being METH-induced NE release in selected brain areas higher than DA release [72]. This makes it likely that NE plays a direct and important role in METH-induced behavioral changes.

In particular, the amount of an oral dose of psychostimulants, which produce amphetamine-type subjective effects in humans, correlates with the potency of these psychostimulants in releasing NE, but not DA, thus suggesting that in humans NE plays a key role in METH addiction [72]. Accordingly, when evaluating the behavioural effects induced by a selective NET blocker in animals, this may reproduce the effects of amphetamines [116]. Lending further implications to these findings, some works have emphasized the role of increased NE release in producing sensitization following METH administration [73].

6.2. NE/DA Interactions

NE activity is critical in regulating the effects of METH on DA neurons encompassing biochemistry, behaviour and neurotoxicity. As reviewed in Section 3, there are a number of brain sites in which NE-DA interactions take place. Areas critical for psychostimulant-induced behaviours, including the NAc, VTA, and PFC, receive a robust LC-NE innervation which alters DA release both in baseline, and above all, following METH administration.

Classic studies on the role of NE on the activity of nigrostriatal DA neurons (reviewed in [117]) demonstrate that endogenous NE affects DA cells at the nigral level by modulating DA neuron firing and DA release after stimulation. In line with this, NE-containing varicosities arising from the LC project through the SN pars compacta [33, 118], and there can be a significant loss of nigral NE after LC damage in mice [26].

The effect of NE on the DA system involves ARs onto DA neurons. In particular, alpha1 ARs are may be critical in certain contingencies involved in the trans-synaptic effects which control the activity of DA neurons in response to D-amphetamine [119].

In fact, the alpha1 AR antagonist prazosin reduces amphetamine-induced hyperlocomotion and sensitization [120-128], possibly through the involvement of the alpha1b AR subtype [124, 127, 128]. The reduced behavioural response to METH found in alpha1b AR knock out (KO) mice is accompanied by a reduced DA release [122, 123, 129] and absence of DA neurotoxicity [130]. Conversely, transgenic mice overexpressing either wild-type or constitutively active alpha1b ARs show nigrostriatal damage associated with serious locomotor dysfunction, tremor at rest, epileptic seizures, and autonomic dysfunctions [131].

The response to psychostimulants produced by modulating the alpha1 AR-mediated NE activity contrasts with data showing an enhanced response to amphetamines found in NE-lacking animals [125, 132, 133].

These findings indicate that specific subtypes of ARs may have contrasting effects on DA neurons. It is thus critical to establish what net influence is produced by NE on the basis that changes in the expression or efficacy of receptor subtypes may lead to unexpected results. The role of ARs in modulating the DA-induced behaviour needs to be clarified and studies are underway to understand the fine mechanisms that regulate the AR-mediated response to psychostimulants.

Regarding mesencephalic DA neurons, NE also modulates VTA DA neurons [53, 54, 119] and there is evidence that NE-containing axons directly project to the VTA and NAc. Thus, it is likely that NE is important for ventral striatal DA release as well. In fact, micro-infusions of either DA or NE directly into the NAc similarly stimulate locomotor activity in rats [134, 135]. In addition to ventral striatum, NE terminals in the PFC play a key role in modulating amphetamine-induced DA release [136], which is critical in rewarding effects, and in reinforcing the behaviour and patterns of compulsive intake by amphetamines [137].

6.3. The Net Effects of NE System on Mesencephalic DA Neurons

Experimental studies aimed at elucidating the role of NE on METH-induced behavioural effects are partly based on animal models involving specific damage to NE systems (Fig. **3**). This systemical approach by-passes the specific effects played by each receptor subtype, and indicates the net effect.

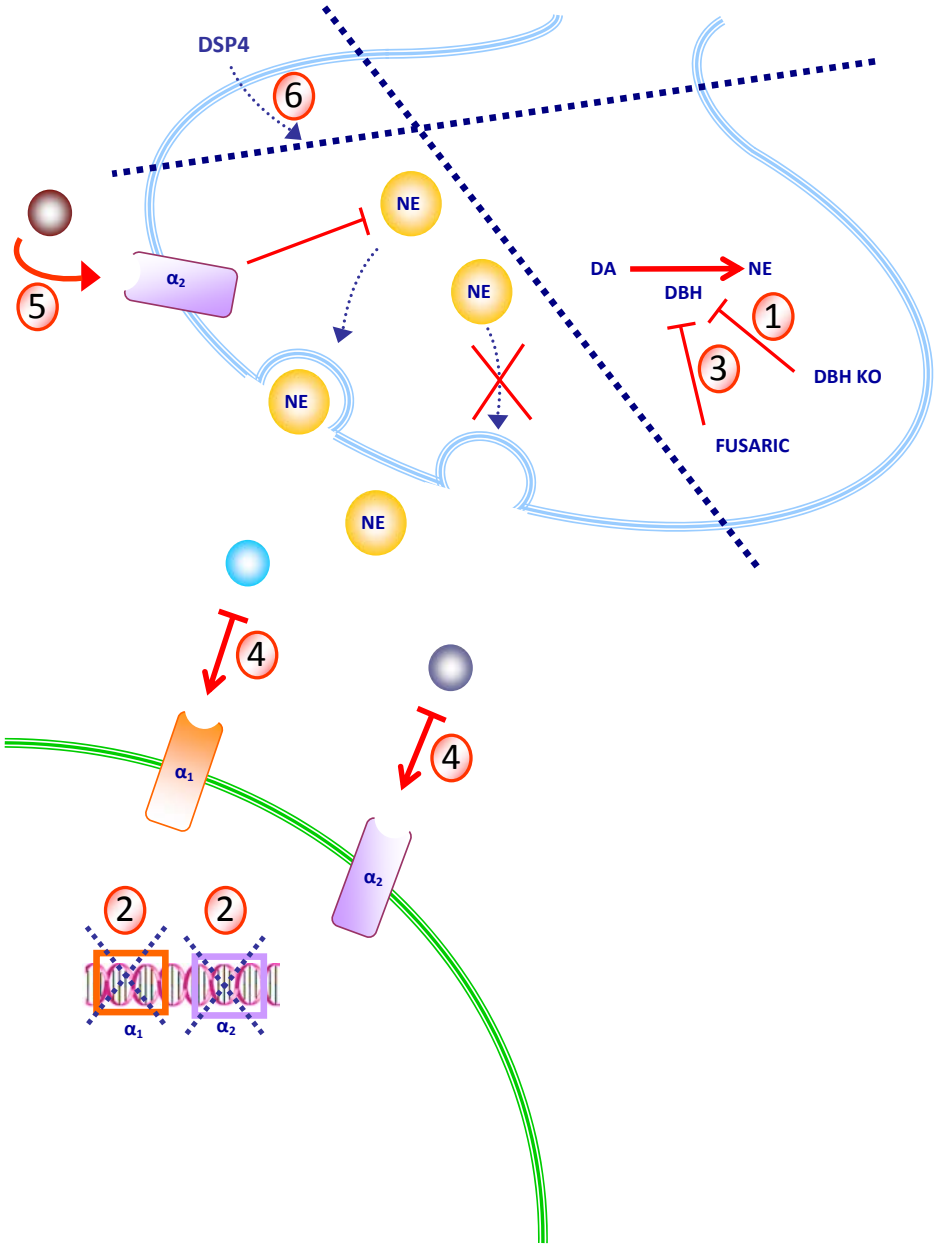

Fig. (3). Experimental tools to suppress/reduce NE activity in the brain. Several experimental approaches can be exploited to suppress/reduce NE activity: 1) genetic ablation of dopamine beta-hydroxylase (DBH), the gene responsible for the conversion of DA into NE; 2) genetic ablation of the genes encoding for NE receptors (alpha1 or alpha2); 3) pharmacological inhibition of DBH by fusaric acid; 4) pharmacological blockade of alpha1 or alpha2 NE receptors; 5) inhibition of NE release by stimulation of pre-synaptic alpha2 receptors; 6) degeneration of locus coeruleus neurons induced by DSP-4. Only the latter mechanism causes the anatomical degeneration of NE neurons specifically arising from locus coeruleus, whereas the other approaches produce a suppression/reduction of NE activity in all brain areas receiving inputs from all NE nuclei. a1, alpha1-adrenoceptor; a2, alpha2-adrenoceptor; DA, dopamine; DBH, dopamine beta-hydroxylase; DBH KO, DBH knock out; NE, norepinephrine.

Norepinephrine tonically inhibits the firing of DA neurons [138]. This occurs through the activation of D2 DA receptors, which work as inhibitory autoreceptors on midbrain DA neurons (Fig. **4A**) [139]. It is thus not surprising that in the absence of NE, the firing rate of these neurons is enhanced and the effects of METH on the mesolimbic (and mesostriatal) system are potentiated (Fig. **4**). Thus the prevalent role of D2 DA receptors explains why in baseline conditions the net effects of NE consists in inhibiting DA neurons (Fig. **4A** and **4B**) [119]. This explains why increased sensitivity of mesencephalic DA neurons to METH following damage to LC occurs.

In fact administration of METH in LC-damaged mice, enhances pulsatile DA release and motor stereotypies [65]. This is confirmed by the enhanced response to METH which

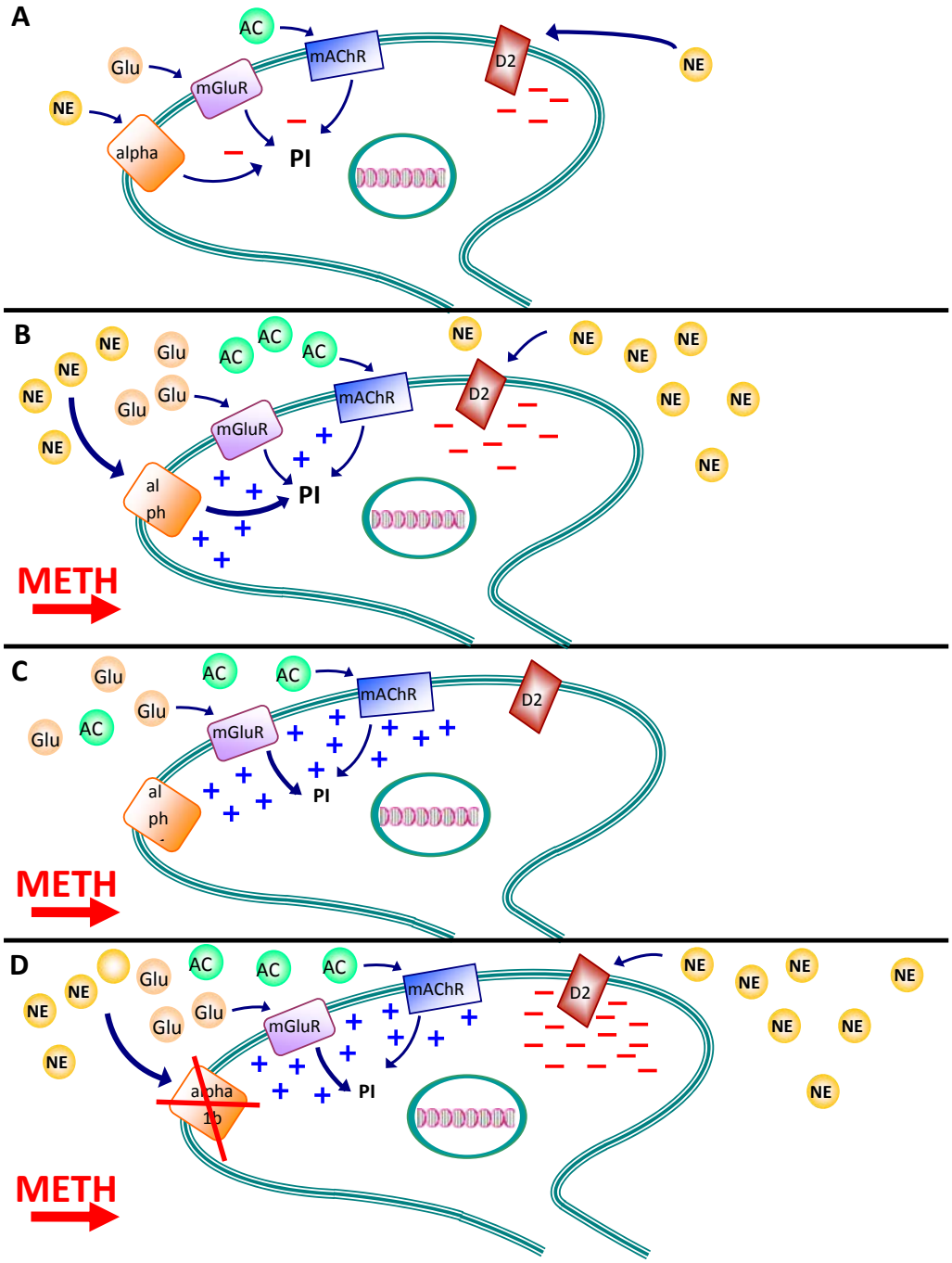

Fig. (4). Effects of NE input on activity of ventral midbrain DA neurons. The figure shows a mesencephalic DA neuron. The main receptors modulating its activity are reported. The final effect on the DA neuron is the result of the degree/type of activation of each receptor subtype depending on the levels of their endogenous ligands in the extracellular space. **A) Basic conditions:** NE produces a long-lasting, tonic inhibition *via* activation of D2 DA autoreceptors placed on neuronal dendrites. At the same time, a short-lasting inhibition of these neurons is produced by metabotropic glutamate receptors (mGluRs), muscarinic receptors (mAChRs), or alpha1 adrenoceptors. These latter three receptor subtypes produce phosphoinositide (PI) hydrolysis. **B) METH administration with intact NE fibers:** METH causes a robust NE release from axon terminals, and D2 and alpha1 adrenoceptors are activated by the excess of extracellular NE. Prolonged activation of alpha1 adrenoceptors depolarizes DA cells directly and indirectly *via* cross-desensitization of the inhibitory mGluRs and mAChRs. This occurs due to the convergence of these receptors to produce the hydrolysis of PI, which in the presence of METH is facilitated by the simultaneous release of NE, glutamate and acetylcholine. However, NE significantly reduces the stimulation of DA neurons by the concomitant activation of D2, which inhibits the firing activity of DA neurons. Therefore, the final effect on DA neurons of such NE release is inhibitory. The prevalence of D2-mediated inhibition over alpha1 adrenoceptors activation is supported by data showing that in the absence of NE, increased methamphetamine-induced DA release occurs [65, 132]. **C) METH administration after NE depletion/lesion:** When METH administration occurs in the absence of NE (induced either by LC fiber lesion or NE synthesis inhibition) the final effect on DA neurons

Fig. (4). contd….

is an enhanced activation, since these neurons are no longer restrained by D2 stimulation by endogenous NE. **D**) **METH administration in the absence of alpha1 adrenoceptors activity:** Alpha1 adrenoceptors antagonists (e.g. prazosin) or knocking out alpha1b adrenoceptors suppress METH-induced DA neuron activation, as testified by a reduction in DA release [129]. Along with this, METH-induced behavioural effects and DA neurotoxicity are prevented [130]. This is further confirmed by the finding that mice overexpressing alpha1b adrenoceptors are characterized by spontaneous nigrostriatal DA toxicity [131]. Alpha1, alpha1 adrenoceptor; Alpha1b, alpha1b adrenoceptors; D2, D2 dopamine receptor; mAChR, muscarinic receptor; METH, methamphetamine; mGluR, metabotropic glutamate receptor; PI, phosphoinositide pathway.

occur in mice carrying a reversible (fusaric acid) and irreversible (DA beta-hydroxylase, DBH, KO mice) NE deficiency (Fig. **3**). This may lead to dramatic behavioural effects such as typical limbic seizures ([132], and our unpublished data). It is likely that METH-induced glutamate release in limbic brain regions may reach the threshold to trigger convulsive seizures in the absence of endogenous NE. In fact, METH is a powerful glutamate releaser [67-69], while NE is considered to be a pivotal endogenous seizure suppressive mechanism [20, 140-143].

7. METHAMPHETAMINE-INDUCED DOPAMINERGIC TOXICITY

The earliest neurochemical effect of amphetamine derivatives is a robust release of the monoamines DA, NE, and serotonin [66]. This leads to a fast depletion of these neurotransmitters, which are drastically reduced in the extracellular compartment just a few hours after the administration of amphetamines [65, 132]. When a single high dose or repetitive low doses of amphetamines derivatives are administered, early acute effects are followed by long-term neurotoxic effects, consisting of damage to DA axonal terminals [144-149].

In both mice and rats, acute repeated injections of METH produce long-lasting decreases in DA levels [145, 149-153], and long-term reductions in several DA markers, such as TH [144, 154, 155], DAT [152, 156, 157], and VMAT-2 [155, 157-159] within the striatum. Morphological studies demonstrate that the persistent loss of integrity of DA biochemical markers is due to the degeneration of DA axon terminals [145-149].

Several studies suggest that the mobilization of endogenous DA plays a key role in producing METH-induced damage to DA axons. In fact, inhibition of DA synthesis prevents METH-induced DA damage [144, 160-162], while treatments that increase cytoplasmic DA levels exacerbate METH neurotoxicity [160, 163, 164].

METH toxicity is thus related to the molecular effects of amphetamines on DA terminals due to effects on DA vesicles, MAO-A and DAT (Fig. **2**). These produce massive amounts of axoplasmic DA, followed by a massive efflux in the extracellular space. The causal link between cytosolic DA levels and METH toxicity is supported by several studies. In fact, overexpression of VMAT2, which stores DA in the vesicles, significantly protects PC12 against METH toxicity [165], while a mutant strain of mice, which possesses only 5-10% of the VMAT2 expressed by wild-type animals, undergo enhanced METH-induced striatal neurotoxicity [166]. For the same reasons, DAT inhibitors protect against METH-induced striatal DA damage [74, 83, 167]. Similar protective effects have been described in the striatum of DAT KO mice [168]. Finally, competitive inhibition of MAO-A increases METH-induced DA [163], while MAO KOs are protected against DA toxicity [77].

When free DA is elevated into the cytoplasm in the presence of MAO inhibition, auto-oxidation leads to the formation of hydrogen peroxide, superoxide radicals and DA quinones [78, 169-172]. These highly reactive compounds trigger a cascade of oxidative reactions leading to irreversible damage in lipids, proteins and organelles [173, 174] within the DA axon terminals and surrounding compartments. In fact, we measured an increase in reactive oxygen species that was associated with the progressive augmentation of DA in METH-treated mice [175]. A variety of mechanisms and molecules are implicated in METH-induced DA axon damage, although the role of DA remains well established.

8. THE ROLE OF NE ON METHAMPHETAMINE-INDUCED DOPAMINERGIC TOXICITY

Enhancement of METH-induced behavioural effects in the absence of NE extends to neurotoxicity. Experimental damage to LC neurons exacerbates DA degeneration induced by amphetamines by (1) enhancing the DA neurotoxic damage, and (2) by reducing the threshold for inducing DA neurotoxic damage. The hypothesis that LC NE neurons protect DA neurons was demonstrated following administration of different amphetamine derivatives [65, 132, 176-178]. In addition, both in mice and rats, LC lesion makes toxic a small dose of METH, not sufficient by itself to produce a nigrostriatal lesion [25, 26].

In keeping with this, animals carrying an inborn NE hyperinnervation of target areas are resistant to DA neurotoxicity [179]. Similarly, pharmacological stimulation of NE neurons provides protection from METH-induced DA neurotoxicity [65].

In order to shed light on whether this increased vulnerability of DA neurons in the presence of a lesion of LC is achieved *via* an acute enhancement of METH toxicity and/or through an impairment of the recovery of the nigrostriatal DA pathway, several different methodological approaches have been used in different animal models. Using intrastriatal microdialysis in rodents, it was found that NE loss enhances the amount of DA released by the nigrostriatal axon terminals after METH [65], demonstrating that LC lesion makes nigrostriatal DA neurons more sensitive to the early acute neurotoxic events induced by METH.

This effect does not depend on the prolonged persistence of METH in the striatum of LC-lesioned animals. In NE-damaged mice, the striatal concentration peak observed one hour after METH injection was unmodified [177]. This appears to rule out NE terminals acting as buffers, which in turn could decrease the availability of METH to DA neurons [64, 180, 181].

As originally postulated in [182], the influence of the LC on the nigrostriatal DA pathway may also involve a cortico-striatal loop. Cortico-striatal fibers are the main glutamatergic input to the neostriatum, and increased striatal glutamate sustains a deleterious effect on nigrostriatal DA axon terminals [68, 183].

Effects extending beyond NE-DA interaction should also be considered. In fact, NE affects the microglial release of specific cytokines [23, 24] and it has been shown that these compounds modulate the viability of mesencephalic neurons [184].

Interestingly, enhancement of METH neurotoxicity is achieved by loss of NE innervation and not only by loss of NE itself. We addressed this aspect by comparing the effects of METH in mice with NE lesions achieved by DSP-4 administration and those with intact NE terminals but specifically lacking NE due to genetic KO or acute pharmacological blockade of the NE biosynthetic enzyme DBH [132]. Dopamine beta-hydroxylase KO and fusaric-acid-treated mice have anatomically intact NE innervation, though are NE deficient. This fact should not be underestimated, since NE terminals contain several co-transmitters, such as adenosine, neuropeptide Y, and galanin, which may modulate METH-induced toxicity. NE co-transmitters, such as galanin, inhibit DA release [185-187].

It is likely that both NE and its co-transmitters are critical since the absence of NE alone, as occurs in DBH KO mice or intact mice, which when treated with fusaric acid, require multiple METH administration to magnify the effects of METH. On the other hand, the anatomical loss of integrity of NE terminals, which is expected to produce a deficiency of both NE and its co-transmitters, worsened the effects of METH already after the first administration [132].

Morphological analysis of striatum in these models provides intriguing results. When observed by electron microscopy, we found membranous multilayer whorls within striatal neurons of NE-depleted mice also in the absence of METH, thus indicating that loss of NE innervation does affect the ultrastructural morphology of striatal neurons [132].

CONCLUSIONS

We have reviewed the role of the NE neurons of LC in mediating the behavioural and neurotoxic effects induced by methamphetamine in the light of recent literature that has reported novel anatomical, electrophysiological, biochemical, behavioural and toxicity data. A variety of morphological connections explain the powerful effects of LC NE neurons on brain areas mediating METH-induced behavioural alterations. These connections justify increasing evidence that highlights that NE is an important neurotransmitter involved in methamphetamine-induced motor alterations and addiction. This concept is amplified by the occurrence of multiple reciprocal connections between NE and DA neurons both at the level of the perikaria (i.e. within mesencephalon and pons) and within target regions, such as the ventral and dorsal striatum, PFC, and several limbic allocortical and nuclear sites. In fact, apart from highlighting that NE plays a direct role in mediating METH-induced behavioural alterations, we believe that this review demonstrates that LC-NE neurons are powerful modulators of the DA system, which plays a pivotal role in mediating the effects of METH in the CNS. This concept is extended to METH-induced neurotoxicity, which is mainly produced against DA-containing neurons and is triggered by DA itself. The modulatory effects of NE on DA availability eventually lead to a powerful effect in modulating METH-induced neurotoxicity. The physiological mechanisms involved and receptor subtypes recruited by these interactions were considered in discussing this topical issue.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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