Role of nitric oxide in psychostimulant-induced neurotoxicity

Valentina Bashkatova¹ and Athineos Philippu²,*

¹ Laboratory of physiology of reinforcement, P.K. Anokhin Institute of Normal Physiology, Moscow, Russia
² Department of Pharmacology and Toxicology, University of Innsbruck, Austria

* Correspondence: Email: athineos.philippou@uibk.ac.at; Tel: +43512292468.

Abstract: In recent decades, consumption of psychostimulants has been significantly increased all over the world, while exact mechanisms of neurochemical effects of psychomotor stimulants remained unclear. It is assumed that the neuronal messenger nitric oxide (NO) may be involved in mechanisms of neurotoxicity evoked by psychomotor stimulants. However, possible participation of NO in various pathological states is supported mainly by indirect evidence because of its short half-life in tissues. Aim of this review is to describe the involvement of NO and the contribution of lipid peroxidation (LPO) and acetylcholine (ACH) release in neurotoxic effects of psychostimulant drugs. NO was directly determined in brain structures by electron paramagnetic resonance (EPR). Both NO generation and LPO products as well as release of ACH were increased in brain structures following four injections of amphetamine (AMPH). Pretreatment of rats with the non-selective inhibitor of NO-synthase (NOS) N-nitro-L-arginine or the neuronal NOS inhibitor 7-nitroindazole significantly reduced increase of NO generation as well as the rise of ACH release induced by AMPH. Both NOS inhibitors injected prior to AMPH had no effect on enhanced levels of LPO products. Administration of the noncompetitive NMDA receptor antagonist dizocilpine abolished increase of both NO content and concentration of LPO products induced by of the psychostimulant drug. Dizocilpine also eliminated the influence of AMPH on the ACH release. Moreover, the neurochemical and neurotoxic effects of the psychostimulant drug sydnocarb were compared with those of AMPH. Single injection of AMPH showed a more pronounced increase in NO and TBARS levels than after an equimolar concentration of sydnocarb. The findings demonstrate the crucial role of NO in the development of neurotoxicity elicited by psychostimulants and underline the key role of NOS in AMPH-induced neurotoxicity.
Keywords: nitric oxide (NO); psychostimulant drugs; neurotoxicity; brain; striatum; electron paramagnetic resonance; amphetamine; Sydnocarb; NO synthase inhibitors; lipid peroxidation; antagonist NMDA glutamate receptor

1. Introduction

Nitric oxide (NO) is a gaseous chemical messenger that participates in varied physiological functions [1,2]. In line with the widespread expression of this pathway, NO participates in various brain functions. NO regulates the activity of neurotransmitter systems of the brain and the content of neuromediators in the extracellular space [3,4]. The role of NO as a biological messenger is determined primarily by its physicochemical properties. It is a highly labile, short-living, reactive free radical [5,6]. The conclusion that NO is a regulatory molecule possessing the properties of a biological messenger was a consequence of the development of numerous scientific fields, including the physiology and pharmacology of the cardiovascular system, toxicology, neurobiology, etc. In recent decades, the role of NO was shown in modeling of central nervous system diseases such as neurodegenerative disorders, stroke, epilepsy, neurotoxic damage [7–12].

The property of NO to cause a biological effect depends to a large extent on the small size of its molecule, its high reactivity, and its ability to diffuse in tissues, including the nervous system. This was the reason to call NO a retrograde messenger [13]. Recently, the importance of NO as a universal modulator in the brain has been postulated [2]. This compound is formed from L-arginine as a result of a two-step reaction of the enzymatic oxidation of its guanidine group to form an intermediate, NG-hydroxy-L-arginine. Several isoforms of NO-synthase (NOS) have been described: constitutive, permanently present in tissue and inducible. Thereby, activity of NOS is important for the manifestation of the physiological and neurochemical action of NO [14,15].

Amphetamine-like psychostimulants, such as amphetamine (AMPH), 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy), and methamphetamine (METH) are psychomotor stimulants that may cause addiction [16]. The mechanism of action of AMPH-like psychostimulants is associated with their ability to influence the monoaminergic systems of the brain. AMPH and its derivatives have a pronounced neurotoxic potential, which is manifested, in particular, in reducing the neuronal content of dopamine (DA), reducing the number of binding sites of the synaptic dopamine transporter [17], degeneration of dopaminergic terminals of the nigrostriatal system [18–21]. Recent reports claim that other brain neurotransmitters, such as glutamate and acetylcholine (ACH) are also involved in the mechanism of neurotoxicity evoked by psychostimulant [2,22–24].

The precise mechanisms of AMPH-induced neurotoxicity remain unclear. Characteristic manifestations of the neurotoxic effect of AMPH and its derivatives, along with the depletion of intracellular DA and degeneration of neurons, are considered to be due to an generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [25–28]. Significant intensification of lipid peroxidation (LPO) processes in the brain was detected after a single injection of METH [29]. Increased generation of hydroxyl radicals as well as elevation of LPO products in rat striatum after AMPH administration has been observed [30]. Similar changes in hydroxyl radicals and LPO have been previously described during convulsions of various genesis as well as during global ischemia in rats [31–33]. It has been suggested that NOS inhibitor methyl N-nitro-L-arginine ester
(L-NAME) [34], or neuronal NOS inhibitor (nNOS) 7-nitroindazole (7-NI) [35] prevent neurotoxic effects of AMPH-like psychostimulants in rats. L-NAME abolishes sensitization to AMPH after short-term and long-term withdrawal [36]. It has also been shown that treatment of newborns with a non-specific NOS inhibitor causes a long-term alternation in the content of NO in the brain with possible consequences for the transmission of DA [37]. Using immunocytochemistry and double in situ hybridization it has been demonstrated that serotonin neurones, which express NOS, are most vulnerable to toxicity induced by substitutes of AMPH such as 3,4-methylenedioxyamphetamine and p-chloroamphetamine [38]. Furthermore, it has been shown that effects of AMPH on basal nNOS mRNA expression in neurons containing nNOS in the striatum depends on dose of the drug [39]. Similarly, the effect of AMPH on the increase in inducible NOS mRNA (iNOS) in highly aggressive proliferating immortalized microglia cells is also concentration-dependent. [40]. Furthermore, it has been shown that repeated administration of MDMA elevates nNOS in the nigrostriatal system.

Aim of this review is to describe the involvement of NO and the contribution of LPO and ACH release in neurotoxic effects elicited by psychostimulant drugs. Furthermore, the effects of equimolar concentrations AMPH and the psychostimulant sydnocrab in on the levels of NO and LPO products in rat brain structures will be delineated.

2. Involvement of NO in neurotoxicity induced by amphetamine

NO levels were determined by electron paramagnetic resonance (EPR). This method allows to determine NO in vivo as a paramagnetic complex in organs and tissues, e.g. liver, heart, tumor etc. [41–43]. The method was slightly modified for detection of NO in brain structures of rats [44]. For our purposes, selective scavenger of NO diethyldithiocarbamate (Sigma, 500 mg/kg, i.p.) and a mixture of FeSO4 (37.5 mg/kg, s.c.) and sodium citrate (165 mg/kg, s.c.) were injected simultaneously and animals were decapitated after 30 minutes. The EPR spectra were recorded at 77 K using a Brucker ESR 300E spectrometer at a frequency of 9.33 kHz, hf-modulation frequency 0.5 mT, microwave power 20 mW and time constant 0.05 s. The concentration of trapped NO was calculated from the intensity of the third ultrafine splitting line of the resonance at g⊥ = 2.035.

We used the following two approaches to study the participation of NO in the development of neurotoxicity evoked by psychomotor stimulants.

2.1. Influence of NOS inhibitors and NMDA antagonist on NO and LPO in brain structures of rats treated with AMPH

Experiments were carried out on a male Sprague-Dawley rats (280–300 g) from the vivarium of University of Innsbruck. Protocols were approved by the Bundesministerium für Wissenschaft, Forschung und Kunst, Austria, Kommission für Tierversuchsanleihgenheiten. Rats were injected with AMPH (Merck, Darmstadt, Germany) four times. The EPR signals of paramagnetic mononitrosyl MNIC–DETC complex registered in the brain cortex of rats are shown in Figure 1. The EPR signal, which represents NO, was enhanced following AMPH administration [45].

Repeated, systemic application of AMPH elevated striatal and cortical NO content (Figure 2A). Administration of the non-competitive NOS inhibitor N-nitro-L-arginine (L-NNA: Sigma, Deisenhofen, Germany) reduced but not abolished the elevation in NO levels evoked by AMPH.
Similarly, the selective nNOS inhibitor 7-Nitroindazole (7-NI) (Sigma, Germany) significantly attenuated the AMPH induced NO generation [46]. The findings demonstrate that endogenous NO is implicated in neurotoxicity elicited by AMPH-like psychostimulants.

**Figure 1.** Typical EPR spectra of the cerebral cortex after administration of DETC and Fe citrate 30 min prior to decapitation. The signals at $g_{\perp}$, $g_{\parallel}$ and $g$ are due to NO-Fe-DETC and reduced iron-sulfur proteins in the mitochondrion respiratory chain. The arrows A, B, C and D indicate the position of components of ultrafine structure of EPR signals from Cu$^{2+}$-DETC complexes at $g_{\perp}$. Arrow direction of B extension of magnetic field [reproduced from Bashkatova et al., 1999].

The interaction of NO with the neurotransmitter glutamate prompted us to study the possible role of this messenger in the pathophysiological mechanisms of AMPH-induced neurotoxicity. The inhibitor of NMDA glutamate receptors dizocilpine (MK-801, Research Biochemical International, Natick, MA, U.S.A.) was administered 30 min prior first AMPH injection. Dizocilpine abolished the rise of NO content induced by four injections of the psychostimulant (Figure 2A) [47]. This finding indicates that NMDA receptors mediate AMPH neurotoxicity and that, as already mentioned, NO is involved in this process.

NO might interact with other radicals, such as ROS. It is known that high doses of AMPH-like psychostimulants lead to an increase in the levels of hydroxyl radicals and LPO products in rat brain [48,49]. Interaction of NO with ROS causes the generation of highly toxic products, in particular, peroxynitrite, which leads to damage and death of neurons [50–52]. However, the possible relationship of these processes is poorly understood. Intensity of LPO processes in brain areas was determined by measuring thiobarbituric acid reactive substances (TBARS). Briefly, tissue
homogenate was mixed with sodium dodecyl sulfate, acetate buffer and thiobarbituric acid. After heating, the pigment was extracted with n-butanol-pyridine mixture and the absorbency was determined at 532 nm [53]. After the last injection of AMPH a more than two-fold increase in TBARS level in the striatum and in the cortex was found [46] (Figure 2B). The NOS inhibitors (L-NNA or 7-NI) administered prior to AMPH failed the increase either striatal, or cortical content of TBARS (Figure 2B). Pretreatment with dizocilpine abolished AMPH-induced elevation of LPO levels in both brain areas (Figure 2B).

These findings are in accordance with our results carried out on the seizure models of rats [54,55] and indicate that both the NO and NO-independent LPO are involved in the neurotoxicity caused by AMPH.

**Figure 2.** Effect of NOS inhibitors (L-NNA, 100 mg/kg, i.p., n = 7 and 7-NI, 50 mg/kg, i.p., n = 6) and NMDA antagonist dizocilpine (1 mg/kg, i.p., n = 6) injected 30 min prior the 1st AMPH injection (5 mg/kg, i.p., injected 4 times every 2 h, n = 6) on NO generation [A] and TBARS content [B] in striatum and cortex of rats. Data are the mean ± SEM. n = amount of rats/group. *P < 0.05, **P < 0.01 compared with the control (vehicle) group; #P < 0.05, ##P < 0.01 compared with AMPH treated rats [to be published].
2.2. Influence of treatment with NOS inhibitors and NMDA antagonist on the ACH release in the nucleus accumbens of rats treated with AMPH

In our experiments the push-pull superfusion technique was used that makes it possible to determine quantitatively ACH released from their neurons in the synaptic cleft in distinct brain areas [47,56]. For the determination of ACH release in the Nac the animals were anaesthetized with urethane, the head was fixed in a stereotaxic frame, and a push-pull cannula (outer tubing: outer diameter 0.83 mm, inner diameter 0.51 mm; inner tubing: outer diameter 0.31 mm, inner diameter 0.16 mm) was stereotaxically inserted through a hole in the skull into the Nac. The Nac was superfused with artificial cerebrospinal fluid which additionally contained neostigmine. The superfusate was continuously collected in time periods of 10 min. The superfusion rate was 20 µl/min. At the end of the experiment the rat was killed with an overdose of sodium phenobarbital and the brain was removed and immersed in formaldehyde solution. ACH was determined in the superfusate by high pressure liquid chromatography (HPLC) with electrochemical detection [56].

The mean basal output of ACH in the nucleus accumbens (NAc) was found to be 25.1 ± 9.1 fmol min⁻¹. Four injections of the vehicle did not influence the release of ACH (Figure 3), while four repeated injections of AMPH led to a dramatic increase in the ACH release rates. The enhanced ACH release reached its maximum 40–120 min after administration of AMPH and persisted to the end of the experiment. NOS inhibitors (Figure 3) as well as the NMDA antagonist (Figure 4) almost completely prevented the increase of ACH release evoked by AMPH.

Very probably, the increase in ACH release following AMPH administration is due to the activation of nNOS. Moreover, the findings point to the crucial role of nNOS in the neurotoxic effects of AMPH. It is still controversial whether NO is functioning as protective agent against neurotoxic effects of AMPH [3,57]. Our results underpin the idea that NO formation prevents neurotoxicity elucidated be AMPH [58].

It has been suggested that glutamatergic neurotransmission is involved in neurotoxicity elicited by AMPH [59–61]. As already mentioned (see 2.1.), the antagonist of NMDA receptor dizocilpine was very effective in reducing the ACH release caused by AMPH. Furthermore, dizocilpine prevented the increase of NO and LPO levels evoked by AMPH. Our results are in accordance with the observation that both NO and NMDA glutamate receptors are implicated in depressive conditions after amphetamine withdrawal [62]. Taken together, the data suggest that activation of NMDA receptors is necessary to induce AMPH neurotoxicity and to modify processes of neurotransmission within NAc.

3. Effects of sydnocarb on NO generation and LPO formation in brain areas of rats: comparison with amphetamine

In clinical practice, the administration of psychostimulants is limited due to a number of side effects, including their neurotoxic action. However, administration of psychostimulants is necessary for the treatment of a number of diseases of the central nervous system, especially in the case of attention deficit hyperactivity syndrome [63–65]. In this regard, the search for new drugs with psychostimulating action, but with less neurotoxicity than amphetamine, is one of the actual problems of modern pharmacology. Sydnocarb (*-phenylisopropyl) -N-phenylecarbamoyl sidnonimine), like other indirect dopaminomimetics, has a wide range of psychoactive
properties [66–68]. Comparison of sydnocarb with METH has shown that the dysfunction of dopaminergic neurotransmission elicited by sydnocarb occurred more slowly and gradually than that of METH [69].

EPR technique was used to compare the effects of two psychostimulant drugs, AMPH and sydnocarb, at the equimolar doses (5 and 23.8 mg/kg, respectively) on the NO level in striatum and cortex of male Sprague Dawley rats (180–210 g) [70]. All experiments were performed in accordance with the French decree No. 87848/19 October 1987 and associated guidelines and the European Community Council directive 86/609/ EEC/ November 1986 (that corresponds to the recent Directive 2010/63/EU). AMPH greatly increased NO levels in the striatum and in the cortex of rats two hours after injection. Sydnocarb also increased NO content, however to a lesser extent than AMPH. Moreover, AMPH evoked more pronounced elevation of LPO products than sydnocarb in both brain areas. Hence, sydnocarb seems to be less neurotoxic than AMPH [70].

Figure 3. Effects of AMPH, of L-NNA and 7-NI on the release of ACH in the Nac. Arrows indicate injections of AMPH (5 mg/kg, i.p.), L-NNA (100 mg/kg, i.p.) and 7-NI (50 mg/kg, i.p.) were administered 30 min prior to the first injection of AMPH. The basal release rate in two samples preceding the first injection of AMPH was taken as 1. *P < 0.05 versus controls. Mean values ± s.e.m., n = 4–6 rats/group. Compounds were administered i.p. so as to make possible comparisons with other findings and to avoid interferences with other factors such as differing absorption rates [reproduced from Bashkatova et al., 1999].
Figure 4. Effects of AMPH and dizocilpine (MK-801) on the release of ACH in the Nac. Arrows indicate injections of AMPH (5 mg/kg, i.p.). Dizocilpine (1 mg/kg, i.p.) was administered 30 min prior to the first injection of AMPH. The basal release rate in two samples preceding the first injection of AMPH was taken as 1. *P < 0.05 versus controls. Mean values ± s.e.m., n = 4–6 rats/group (reproduced from Kraus et al., 2002).

These findings are consistent with recent studies that AMPH has a significantly higher impact on the parameters of the stereotypical behavior of rats [71]. The maximum level of stereotypy (6 scores) was achieved within 2 hours after the first injection of the drug. Sydnocarb also caused motor stereotypy, but its intensity was significantly lower than that of AMPH (4 scores). Moreover, sydnocarb led to a slow and gradual increase of the parameters of dopaminergic dysfunction in comparison with AMPH [72]. Moreover, treatment with sydnocarb was accompanied by a less pronounced increase in formation of OH in comparison with that after AMPH administration [73]. It has been established that increased formation of free radicals induces LPO, which is considered to be one of indexes of neurotoxicity [74,75]. Our findings demonstrate that AMPH as well as sydnocarb enhance NO generation and TBARS formation in rat brain. Finally, our results suggest that in striatum and cerebral cortex, AMPH, and to a lesser degree sydnocarb, may elicit neurotoxicity.

Taken together, these findings confirm that NO and ROS play important role in processes of neurotoxicity evoked by AMPH and sydnocarb. Furthermore, they point to the key role of neuronal NOS in AMPH-induced neurotoxicity— and demonstrate the crucial role of NO in neurotoxicity induced by psychostimulant drugs.

Conflict of interest

All authors declare no conflicts of interest in this paper.
References

1. Dawson TM, Snyder SH (1994) Gases as biological messengers: nitric oxide and carbon monoxide in the brain. *J Neurosci* 14: 5147–5159.
2. Moncada S, Higgs EA (1991) Endogenous nitric oxide: physiology, pathology and clinical relevance. *Eur J Clin Invest* 21: 361–374.
3. Philippu A (2016) Nitric Oxide: A universal modulator of brain function. *Curr Med Chem* 23: 2643–2652.
4. Garthwaite J (2019) NO as a multimodal transmitter in the brain: discovery and current status. *Br J Pharmacol* 176: 197–211.
5. Ignarro LJ (1990) Nitric oxide. A novel signal transduction mechanism for transcellular communication. *Hypertension* 16: 477–483.
6. Möller MN, Cuevasanta E, Orrico F, et al. (2019) Diffusion and transport of reactive species across cell membranes. *Adv Exp Med Biol* 1127: 3–19.
7. Li H, Förstermann U (2000) Nitric oxide in the pathogenesis of vascular disease. *J Pathol* 190: 244–254.
8. Prast H, Philippu A (2001) Nitric oxide as a modulator of neuronal function. *Prog Neurobiol* 64: 51–68.
9. Mukherjee P, Cinelli MA, Kang S, et al. (2014) Development of nitric oxide synthase inhibitors for neurodegeneration and neuropathic pain. *Chem Soc Rev* 43: 6814–6838.
10. Capannolo M, Ciccarelli C, Molteni R, et al. (2014) Nitric oxide synthase inhibition reverts muscarinic receptor down-regulation induced by pilocarpine- and kainic acid-evoked seizures in rat fronto-parietal cortex. *Epilepsy Res* 108: 11–19.
11. Watanabe S, Kumazaki S, Yamamoto S, et al. (2018) Non-alcoholic steatohepatitis aggravates nitric oxide synthase inhibition-induced arteriosclerosis in SHRSP5/Dmcr rat model. *Int J Exp Pathol* 99: 282–294.
12. Woodard A, Barbery B, Wilkinson R, et al. (2019) The role of neuronal nitric oxide and its pathways in the protection and recovery from neurotoxin-induced de novo hypokinetic motor behaviors in the embryonic zebrafish (Danio rerio). *AIMS Neuroscience* 6: 25–42.
13. Breedt DS, Snyder SH (1994) Nitric oxide: A physiologic messenger molecule. *Annu Rev Biochem* 63: 175–195.
14. Sorokin A (2016) Nitric oxide synthase and cyclooxygenase pathways: A complex interplay in cellular signaling. *Curr Med Chem* 23: 2559–2578.
15. Balke JE, Zhang L, Percival JM (2019) Neuronal nitric oxide synthase (nNOS) splice variant function: Insights into nitric oxide signaling from skeletal muscle. *Nitric Oxide* 82: 35–47.
16. Teixeira-Gomes A, Costa VM, Feio-Azevedo R, et al. (2015) The neurotoxicity of amphetamines during the adolescent period. *Int J Dev Neurosci* 41: 44–62.
17. Jones SR, Joseph JD, Barak LS, et al. (1999) Dopamine neuronal transport kinetics and effects of amphetamine. *J Neurochem* 73: 2406–2414.
18. Gibb JW, Johnson M, Hanson GR (1990) Neurochemical basis of neurotoxicity. *Neurotoxicol* 11: 317–321.
19. 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.
20. Siciliano CA, Calipari ES, Ferris MJ, et al. (2014) Biphasic mechanisms of amphetamine action at the dopamine terminal. *J Neurosci* 34: 5575–5582.

21. O'Dell SJ, Weihmuller FB, Marshall JF (1991) Multiple methamphetamine injections induce marked increases in extracellular striatal dopamine which correlate with subsequent neurotoxicity. *Brain Res* 564: 256–260.

22. Nash JF, Yamamoto BK (1993) Effect of D-amphetamine on the extracellular concentrations of glutamate and dopamine in iprindole-treated rats. *Brain Res* 627: 1–8.

23. Hussain RJ, Taraschenko OD, Glick SD (2008) Effects of nicotine, methamphetamine and cocaine on extracellular levels of acetylcholine in the interpeduncular nucleus of rats. *Neurosci Lett* 440: 270–274.

24. Mabrouk OS, Semaan DZ, Mikelman S, et al. (2014) Amphetamine stimulates movement through thalamocortical glutamate release. *J Neurochem* 128: 152–161.

25. Abekawa T, Ohmori T, Honda M, et al. (2001) Effect of low doses of L-NAME on methamphetamine-induced dopaminergic depletion in the rat striatum. *J Neural Transm* 108: 1219–1230.

26. Pereira FC, Macedo TR, Imam SZ, et al. (2004) Lack of hydroxyl radical generation upon central administration of methamphetamine in rat caudate nucleus: A microdialysis study. *Neurotox Res* 6: 149–152.

27. Shenouda SK, Varner KJ, Carvalho F, et al. (2009) Metabolites of MDMA induce oxidative stress and contractile dysfunction in adult rat left ventricular myocytes. *Cardiovasc Toxicol* 9: 30–38.

28. Salum C, Schmidt F, Michel PP, et al. (2016) Signaling mechanisms in the Nitric Oxide donor- andamphetamine-induced dopamine release in mesencephalic primary cultured neurons. *Neurotox Res* 29: 92–104.

29. Acikgoz O, Gonenc S, Kayatekin BM, et al. (2000) The effects of single dose of methamphetamine on lipid peroxidation levels in the rat striatum and prefrontal cortex. *Eur Neuropsychopharmacol* 10: 415–418.

30. Wan FJ, Lin HC, Huang KL, et al. (2000) Systemic administration of d-amphetamine induces long-lasting oxidative stress in the rat striatum. *Life Sci* 66: 205–212.

31. Raevskii KS, Bashkatova VG, Narkevich VB, et al. (1998) Nitric oxide in the rat cerebral cortex in seizure models: potential ways of pharmacological modulation. *Ross Fiziol Zh Im I M Sechenova* 84: 1093–1099.

32. Bashkatova VG, Vitskova Glu, Narkevich VB, et al. (1999) The effect of anticonvulsants on the nitric oxide content and level of lipid peroxidation in the brain of rats in model seizure states. *Eksp Klin Farmakol* 62: 31–34.

33. Fadiukova OE, Alekseev AA, Bashkatova VG, et al. (2001) Semax prevents elevation of nitric oxide generation caused by incomplete global ischemia in the rat brain. *Eksp Klin Farmakol* 64: 31–34.

34. Zheng Y, Laverty R (1998) Role of brain nitric oxide in (+/−)3,4-methylenedioxymethamphetamine (MDMA)-induced neurotoxicity in rats. *Brain Res* 795: 257–263.

35. Itzhak Y, Martin JL, Ail SF (2000) nNOS inhibitors attenuate methamphetamine-induced dopaminergic neurotoxicity but not hyperthermia in mice. *Neuroreport* 11: 2943–2946.
36. Liu YP, Tung CS, Lin PJ, et al. (2011) Role of nitric oxide in amphetamine-induced sensitization of schedule-induced polydipsic rats. *Psychopharmacology (Berl)* 218: 599–608.

37. Morales-Medina JC, Mejorada A, Romero-Curiel A, et al. (2008) Neonatal administration of N-omega-nitro-L-arginine induces permanent decrease in NO levels and hyperresponsiveness to locomotor activity by D-amphetamine in postpubertal rats. *Neuropharmacology* 55: 1313–1320.

38. De Silva DJ, French SJ, Cheung NY, et al. (2005) Rat brain serotonin neurones that express neuronal nitric oxide synthase have increased sensitivity to the substituted amphetamine serotonin toxins 3,4-methylenedioxymethamphetamine and p-chloroamphetamine. *Neuroscience* 134: 1363–1375.

39. Wang JQ, Lau YS (2001) Dose-related alteration in nitric oxide synthase mRNA expression induced by amphetamine and the full D1 dopamine receptor agonist SKF-82958 in mouse striatum. *Neurosci Lett* 311: 5–8.

40. Tocharus J, Chongthammakun S, Govitrapong P (2008) Melatonin inhibits amphetamine-induced nitric oxide synthase mRNA overexpression in microglial cell lines. *Neurosci Lett* 439: 134–137.

41. Kleschyov AL, Sedov KR, Mordvintcev PI, et al. (1994) Biotransformation of sodium nitroprusside into dinitrosyl iron complexes in tissue of ascites tumors of mice. *Biochem Biophys Res Commun* 202: 168–173.

42. Vanin AF, Huisman A, van Faassen EE (2002) Iron dithiocarbamate as spin trap for nitric oxide detection: pitfalls and successes. *Methods Enzymol* 359: 27–42.

43. Hogg N (2010) Detection of nitric oxide by electron paramagnetic resonance spectroscopy. *Free Radic Biol Med* 49: 122–129.

44. Bashkatova VG, Mikoian VD, Kosacheva ES, et al. (1996) Direct determination of nitric oxide in rat brain during various types of seizures using ESR. *Dokl Akad Nauk* 348: 119–121.

45. Bashkatova V, Kraus M, Prast H, et al. (1999) Influence of NOS inhibitors on changes in ACH release and NO level in the brain elicited by amphetamine neurotoxicity. *Neuroreport* 10: 3155–3158.

46. Bashkatova V, Kraus MM, Vanin A, et al. (2005) 7-Nitroindazole, nNOS inhibitor, attenuates amphetamine-induced amino acid release and nitric oxide generation but not lipid peroxidation in the rat brain. *J Neural Transm* 112: 779–788.

47. Kraus MM, Bashkatova V, Vanin A, et al. (2002) Dizocilpine inhibits amphetamine-induced formation of nitric oxide and amphetamine-induced release of amino acids and acetylcholine in the rat brain. *Neurochem Res* 27: 229–235.

48. Wan FJ, Tung CS, Shiah IS, et al. (2006) Effects of alpha-phenyl-N-tert-butyl nitrotrone and N-acetylcysteine on hydroxyl radical formation and dopamine depletion in the rat striatum produced by d-amphetamine. *Eur Neuropsychopharmacol* 16: 147–153.

49. Kita T, Miyazaki I, Asanuma M, et al. (2009) Dopamine-induced behavioral changes and oxidative stress in methamphetamine-induced neurotoxicity. *Int Rev Neurobiol* 88: 43–64.

50. Dawson TM, Dawson VL, Snyder SH (1994) Molecular mechanisms of nitric oxide actions in the brain. *Ann N Y Acad Sci* 738: 76–85.

51. Li J, Baud O, Vartanian T, et al. (2005) Peroxynitrite generated by inducible nitric oxide synthase and NADPH oxidase mediates microglial toxicity to oligodendrocytes. *Proc Natl Acad Sci U S A* 102: 9936–9941.
52. Ali SF, Imam SZ, Itzhak Y (2005) Role of peroxynitrite in methamphetamine-induced dopaminergic neurodegeneration and neuroprotection by antioxidants and selective NOS inhibitors. *Ann N Y Acad Sci* 1053: 97–98.

53. Ohkawa H, Ohishi N, Yagi K (1979) Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Anal Biochem* 95: 351–358.

54. Bashkatova V, Vitskova G, Narkevich V, et al. (2000) Nitric oxide content measured by ESR-spectroscopy in the rat brain is increased during pentylenetetrazole-induced seizures. *J Mol Neurosci* 14: 183–190.

55. Klyueva YYu, Chepurnov SA, Chepurnova NE, et al. (2001) Role of nitric oxide and lipid peroxidation in mechanisms of febrile convulsions in wistar rat pups. *Bull Exp Biol Med* 131: 47–49.

56. Prast H, Fischer H, Werner E, et al. (1995) Nitric oxide modulates the release of acetylcholine in the ventral striatum of the freely moving rat. *Naunyn-Schmiedeberg’s Arch Pharmacol* 352: 67–73.

57. Issy AC, Dos-Santos-Pereira M, Pedrazzi JFC, et al. (2018) The role of striatum and prefrontal cortex in the prevention of amphetamine-induced schizophrenia-like effects mediated by nitric oxide compounds. *Prog Neuropsychopharmacol Biol Psychiatry* 86: 353–362.

58. Salum C, Guimarães FS, Brandão ML, et al. (2006) Dopamine and nitric oxide interaction on the modulation of prepulse inhibition of the acoustic startle response in the Wistar rat. *Psychopharmacology (Berl)* 185: 133–141.

59. Somsalla PK, Nicklas WJ, Heikkila RE (1989) Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. *Science* 243: 398–400.

60. Tata DA, Yamamoto BK (2007) Interactions between methamphetamine and environmental stress: role of oxidative stress, glutamate and mitochondrial dysfunction. *Addiction* 102: 49–60.

61. Li MH, Underhill SM, Reed C, et al. (2017) Amphetamine and methamphetamine increase NMDAR-GluN2B synaptic currents in midbrain dopamine neurons. *Neuropsychopharmacology* 42: 1539–1547.

62. Haj-Mirzaian A, Amiri S, Amini-Khoei H, et al. (2018) Involvement of NO/NMDA-R pathway in the behavioral despair induced by amphetamine withdrawal. *Brain Res Bull* 139: 81–90.

63. Erenberg G (2005) The relationship between tourette syndrome, attention deficit hyperactivity disorder, and stimulant medication: a critical review. *Semin Pediatr Neurol* 12: 217–221.

64. Jain R, Jain S, Montano CB (2017) Addressing diagnosis and treatment gaps in adults with attention-deficit/hyperactivity disorder. *Prim Care Companion CNS Disord* 19: pii: 17nr02153.

65. Quilty LC, Allen TA, Davis C, et al. (2019) A randomized comparison of long acting methylphenidate and cognitive behavioral therapy in the treatment of binge eating disorder. *Psychiatry Res* 273: 467–474.

66. Novoselov IA, Cherepov AB, Raevskii KS, et al. (2002) Locomotor activity and expression of c-Fos protein in the brain of C57BL and Balb/c mice: effects of D-amphetamine and sydnocarb. *Eksp Klin Farmakol* 65: 18–21.

67. Gruner JA, Mathiasen JR, Flood DG, et al. (2011) Characterization of pharmacological and wake-promoting properties of the dopaminergic stimulant sydnocarb in rats. *J Pharmacol Exp Ther* 337: 380–390.

68. Gainetdinov RR, Sotnikova TD, Grekhova TV, et al. (1997) Effects of a psychostimulant drug sydnocarb on rat brain dopaminergic transmission in vivo. *Eur J Pharmacol* 340: 53–58.
69. Afanas’ev II, Anderzhanova EA, Kudrin VS, et al. (2001) Effects of amphetamine and sydnocarb on dopamine release and free radical generation in rat striatum. *Pharmacol Biochem Behav* 2001:69: 653–658.

70. Bashkatova V, Mathieu-Kia AM, Durand C, et al. (2002) Neurochemical changes and neurotoxic effects of an acute treatment with sydnocarb, a novel psychostimulant: comparison with D-amphetamine. *Ann N Y Acad Sci* 965: 180–192.

71. Feier G, Valvassori SS, Lopes-Borges J (2012) Behavioral changes and brain energy metabolism dysfunction in rats treated with methamphetamine or dextroamphetamine. *Neurosci Lett* 530: 75–79.

72. Witkin JM, Savtchenko N, Mashkovsky M, et al. (1999) Behavioral, toxic, and neurochemical effects of sydnocarb, a novel psychomotor stimulant: comparisons with methamphetamine. *J Pharmacol Exp Ther* 288: 1298–1310.

73. Anderzhanova EA, Afanas'ev II, Kudrin VS, et al. (2000) Effect of d-amphetamine and sydnocarb on the extracellular level of dopamine, 3,4-dihydroxyphenylacetic acid, and hydroxyl radicals generation in rat striatum. *Ann N Y Acad Sci* 914: 137–145.

74. Chen N, Li J, Li D, et al. (2014) Chronic exposure to perfluorooctane sulfonate induces behavior defects and neurotoxicity through oxidative damages, in vivo and in vitro. *PLoS One* 9: e113453.

75. Zhang LP, Wang QS, Guo X, et al. (2007) Time-dependent changes of lipid peroxidation and antioxidative status in nerve tissues of hens treated with tri-ortho-cresyl phosphate (TOCP). *Toxicology* 239: 45–52.

© 2019 the Author(s), licensee AIMS Press. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0)