Published in final edited form as:
Neurotox Res. 2014 February ; 25(2): . doi:10.1007/s12640-013-9415-2.

Is There A Role for Nitric Oxide in Methamphetamine-Induced Dopamine Terminal Degeneration?

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Abstract

Methamphetamine (METH) abuse results in long-term damage to the dopaminergic system, manifesting as decreases in dopamine (DA) tissue content, DA transporter (DAT) binding, as well as tyrosine hydroxylase (TH) and vesicular monoamine transporter (VMAT) immunostaining. However, the exact cascade of events that ultimately results in this damage has not been clearly elucidated. One factor that has been heavily implicated in METH-induced DA terminal degeneration is the production of nitric oxide (NO). Unfortunately, many of the studies attempting to clarify the role of NO in METH-induced neurotoxicity have been confounded by issues such as the disruption of METH-induced hyperthermia, preventing the formation of strong conclusions. As a result, there is a body of work suggesting that NO is sufficient for METH-induced neurotoxicity, while other studies suggest that NO does not play a role in METH-induced degeneration of DA nerve terminals. This review summarizes the existing studies investigating the role of NO in METH-induced neurotoxicity, and argues that while NO may be necessary for METH-induced neurotoxicity, it is not sufficient. Finally, important areas of future investigation are highlighted and discussed.

Keywords

Dopamine; Methamphetamine; Neurotoxicity Nitric Oxide; Nitric Oxide Synthase

Methamphetamine (METH) abuse continues to be a significant public health concern in the United States. According to the National Survey on Drug Use and Health, approximately 12 million Americans report using METH at least once in their lifetime (SAMHSA/OSM, 2011). Additionally, new evidence indicates that individuals with a history of METH abuse have an increased risk for developing Parkinson's Disease, compared to both healthy controls and individuals with a history of cocaine use (Callaghan et al., 2010; Callaghan et al., 2012). Thus, abuse of amphetamines, and METH in particular, continues to be a significant public health concern and will remain a significant burden to society for years to come. Importantly, exposure to high doses or repeated administration of METH results in long-lasting damage to the dopamine (DA) system. This damage includes reduced levels of DA (Kogan et al., 1976; Wagner et al., 1980), tyrosine hydroxylase (TH; (Kogan et al., 1976), dopamine transporter (DAT; (Volkow et al., 2001a; Volkow et al., 2001b; McCann et

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al., 2008), and vesicular monoamine transporter levels (VMAT; (Guilarte et al., 2003) in human METH abusers and animal models. Given the high rates of abuse, as well as the significant damage to the DA system that occurs with METH exposure, studies elucidating factors associated with METH-induced neurotoxicity are essential for prevention of the toxicity and for the development of therapeutic treatments for individuals with a history of METH abuse. One factor that has been heavily implicated in METH-induced neurotoxicity is the production of nitric oxide (NO). This review summarizes the work examining the role of NO in METH-induced neurotoxicity and suggests areas of future study.

Nitric Oxide and Nitric Oxide Synthase

Nitric oxide is a gaseous neuromodualator implicated in various physiological processes, including neuroplasticity (Wang et al., 2005; Serulle et al., 2007), neurovascular coupling (Faraci and Breese, 1993), and neuronal excitability (Centonze et al., 2001; West and Grace, 2004). However, NO has also been implicated in neuronal damage (Louin et al., 2006; Mohammadi et al., 2012) and various central nervous system (CNS) diseases including Alzheimer's disease (Sultana et al., 2006), Parkinson's disease (Hunot et al., 1996), and Multiple Sclerosis (Bo et al., 1994), suggesting that in addition to playing a role in normal CNS function, NO may also play a role in neurodegeneration.

Nitric oxide is synthesized by a family of proteins termed nitric oxide synathase (NOS), of which there are three distinct isoforms. The two constitutively expressed, Ca^{2+}-dependent isoforms are neuronal nitric oxide synthase (nNOS or NOS-I) and endothelial nitric oxide synthase (eNOS or NOS-III; (Bredt and Snyder, 1990; Forstermann et al., 1991). These two isoforms are basally expressed in their respective cell types under normal conditions. In the brain, nNOS is predominately expressed by neurons (Bredt et al., 1990; Bredt and Snyder, 1990), although some data suggest possible astrocytic expression of nNOS, as well (Arbones et al., 1996). Importantly, in striatum, nNOS is expressed by a subpopulation of interneurons that co-express GABA, somatostatin (SST), and neuropeptide Y (Kawaguchi et al., 1995; Figueredo-Cardenas et al., 1996). Endothelial nitric oxide synthase is expressed predominantly by endothelial cells (Seidel et al., 1997; Stanarius et al., 1997), although neuronal expression in hippocampus (Dinerman et al., 1994; O'Dell et al., 1994) and astrocytic expression (Lin et al., 2007) have also been described. The third isoform, inducible nitric oxide synthase (iNOS or NOS-II), is not basally expressed under normal conditions, but rather is transcriptionally induced and activated in a Ca^{2+}-independent manner (Yui et al., 1991) during inflammatory reactions via a cytokine-mediated cascade (Lowenstein et al., 1993; Xie et al., 1993; Lin and Murphy, 1997; Park et al., 1997). Inducible nitric oxide synthase is expressed mainly by astrocytes, microglia, and macrophages throughout the brain (Endoh et al., 1994; Liu et al., 1996). Therefore, although all three isoforms convert the precursor L-arginine to NO and L-citrulline, each isoform arises from a different gene product (Janssens et al., 1992; Geller et al., 1993; Hall et al., 1994) with unique expression patterns.

Under normal conditions, NO plays a role in normal physiological processes; however, over-production of NO may result in CNS damage. For example, under normal conditions, NO is known to bind soluble guanylate cyclase (sGC) resulting in activation of the enzyme, cyclic guanosine monophosphate (cGMP) production, and activation of cellular events downstream of cGMP (Stone and Marletta, 1996). However, NO has also been heavily implicated in several CNS injuries and neurodegenerative diseases. In particular, NO can interact with superoxide (0_2) to form peroxynitrite ($ONOO^-$; (Beckman et al., 1990), a potent oxidant (Radi et al., 1991). Peroxynitrite, in turn, can interact with various cellular targets, resulting in protein nitration, lipid peroxidation (Rubbo et al., 1994), and DNA damage (Salgo et al., 1995; Yermilov et al., 1995; Yermilov et al., 1996). More specifically,

peroxynitrite can interrupt cellular respiration by inhibiting components of the mitochondrial electron transport chain, including complexes I and III (Radi et al., 1994; Clementi et al., 1998; Riobo et al., 2001). NO can also directly nitrate proteins, resulting in protein/enzyme malfunction (Konorev et al., 1998; Blanchard-Fillion et al., 2001). Thus, while it is clear that NO is an important mediator of normal physiological processes, NO can also be detrimental to cellular function, and overproduction of NO can thus contribute to cellular injury.

To date, several studies have described increased NO production following METH exposure. For example, detection of nitrated proteins, an indirect measure of peroxynitrite formation, is increased in striatum following METH exposure (Imam et al., 1999; Imam et al., 2000; Anderson and Itzhak, 2006; Wang et al., 2008; Friend et al., 2013). Our lab has also shown an increase in NADPH diaphorase histochemical staining (Friend et al., 2013), a measure of NOS activity (Dawson et al., 1991; Hope et al., 1991), following exposure to a neurotoxic regimen of METH. Furthermore, the co-administration of peroxynitrite decomposition catalysts or NOS inhibitors is reported to result in decreased NO production following METH exposure (Imam et al., 1999; Imam et al., 2000). Thus, it is apparent that METH results in NO production.

Source of Nitric Oxide Following Methamphetamine Exposure

Given the increase in NO production following METH exposure and data suggesting roles for NO and peroxynitrite in neurodegeneration, several studies have attempted to identify which isoform of NOS contributes to the METH-induced NO production. One study examined nNOS and iNOS expression in striatum and found that nNOS protein, as well as the number of cells positive for NADPH-diaphorase histochemical staining, were increased following METH exposure (Deng and Cadet, 1999). However, since this study was published, our lab and others have examined nNOS expression via immunohistochemistry (Wang and Angulo, 2011) or *in situ* hybridization (Friend et al., 2013) and have failed to see any change in the amount of nNOS expression at either the mRNA or protein level. Additionally, we also examined the number of cells with histochemical staining for NADPH diaphorase—a stain produced by the enzymatic activity of NOS (Hope et al., 1991)—and again, we did not observe a METH-induced change in the number of cells positively stained. It is possible that the discrepancy between the studies reflect a mouse *vs*. rat difference, as differences in nNOS expression have been observed between species and strains of animals within a species (Blackshaw et al., 2003). Furthermore, it is generally accepted that nNOS is constitutively expressed and that NO production via nNOS arises as a consequence of Ca^{2+}-calmodulin and Ca^{2+} influx through NMDA receptors (Bredt and Snyder, 1990; Sattler et al., 1999). In fact, although we have not observed changes in the numbers of cells expressing nNOS mRNA or the number of cells positive for NADPH diaphorase histochemical staining, we did observe an increase in total NADPH diaphorase histochemical staining (*i.e*. percent of the total imaged field with signal; (Friend et al., 2013). These data suggest that METH increases NO production via activation of constitutively expressed nNOS rather than a change in its expression.

Inducible nitric oxide synthase expression has also been examined following a neurotoxic regimen of METH, and no induction of iNOS protein was observed (Deng and Cadet, 1999). However, Deng and Cadet examined iNOS expression at 1hr, 24hr, and 1 week following exposure to a neurotoxic regimen of METH—time points at which glial cells, the cell types in which induction of iNOS mRNA expression typically occurs (Gibson et al., 2005), may not be fully reactive (LaVoie et al., 2004). Therefore, we examined iNOS mRNA expression in animals 1 hr and also 48 hr following a neurotoxic regimen of METH, as glial reactivity is maximal at 48 hr after exposure to a neurotoxic regimen of METH (LaVoie et al., 2004). Consistent with the data from Deng and Cadet (Deng and Cadet, 1999), we also failed to see

any induction of iNOS mRNA (Friend et al., 2013). Thus, because iNOS must be transcriptionally induced in order to produce NO (Lowenstein et al., 1993; Xie et al., 1993), these data suggest that NO is not produced via iNOS after exposure to a neurotoxic regimen of METH.

Finally, our lab is the first to have examined eNOS mRNA expression following a neurotoxic regimen of METH. As was the case for iNOS, we did not observe any change in eNOS expression in animals sacrificed 1 hr or 48 hr after exposure to the neurotoxic regimen of METH (Friend et al., 2013). However, given that eNOS is also constitutively expressed, there remains the possibility that eNOS may contribute, at least in part to METH-induced NO production. In this regard, our data show that when we limit our analysis of NOS activity to the nNOS expressing interneurons in striatum by excluding blood vessels from the analysis of the NADPH diaphorase histochemical staining, we still observe an increase in NOS activity, suggesting that eNOS expressing endothelial cells are not contributing to METH-induced increases in NOS activation. Taken together, these data suggest that nNOS, rather than eNOS, is the source of NO production in response to METH exposure. However, a better general understanding of how the constitutively expressed NOS isoforms are regulated will lead to a more definitive answer regarding the particular isoforms responsible for METH-induced NO production. For instance, studies examining NO in the context of long-term potentiation (LTP) in the hippocampus have demonstrated compensatory interactions between nNOS and eNOS. These data show that LTP is disrupted only if both nNOS and eNOS are eliminated (Son et al., 1996), suggesting that in the absence of one isoform of NOS the other may suffice in generating the NO necessary for LTP to occur. If a similar scenario exists in the context of METH-induced neurotoxicity, then it is conceivable that either isoform may contribute to METH-induced increases in NO.

Nitric Oxide in Methamphetamine-Induced Neurotoxicity

Several attempts have been made to elucidate the role of NO in METH-induce DA nerve terminal degeneration by using either pharmacological or genetic manipulations. Unfortunately, these studies have been inconclusive. For example, the co-administration of peroxnitrite decomposition catalysts with METH protects against METH-induced DA depletions (Imam et al., 1999). Furthermore, studies using genetic manipulations have shown that METH-induced DA depletions are blocked in mice with deletion of nNOS (Itzhak et al., 1998; Itzhak et al., 2000b) and partially attenuated in mice with deletion of iNOS (Itzhak et al., 1999; Itzhak et al., 2000b), suggesting a role for NO and its downstream mediator, peroxynitrite, in METH-induced neurotoxicity. However, although the use of peroxynitrite decomposition catalysts or the use of nNOS and iNOS knockout mice afforded protection against the neurotoxic effects of METH, these manipulations also mitigated the METH-induced hyperthermia (Itzhak et al., 1998; Imam et al., 1999; Itzhak et al., 1999) known to be tightly associated METH-induced monoamine toxicity (Ali et al., 1994; Bowyer et al., 1994). In fact, simply cooling animals during METH exposure protects animals against METH-induced toxicity (Ali et al., 1994). Therefore it is difficult to determine whether the attenuation of neurotoxicity is a result of the manipulations of the NOS system or whether it arose from the mitigation of METH-induced hyperthermia. Finally, while some studies suggest protection against METH-induced DA depletions when NOS inhibitors are co-administered with METH (Di Monte et al., 1996; Itzhak and Ali, 1996; Ali and Itzhak, 1998; Itzhak et al., 2000a), others suggest that the neuroprotective effects of NOS inhibitors simply result from mitigation of METH-induced hyperthermia (Taraska and Finnegan, 1997; Callahan and Ricaurte, 1998). Therefore, results from the work using pharmacological inhibition of NOS in the context of METH-induced neurotoxicity remain inconclusive. Conducting these studies while carefully controlling for METH-induced hyperthermia (*i.e.* placing knockout animals in an environment with

increased ambient temperature to maintain METH-induced hyperthermia) should lead to more conclusive results in this regard. Additionally, studies using knockdown approaches, particularly in specific cell types, (*e.g*. shRNA driven by cell type specific promoters such as SST) should more clearly elucidate not only the NOS isoform contributing to increased NO during exposure to METH, but also the particular cell population involved.

Adding further debate to the role of NO in METH-induced neurotoxicity are studies that use other manipulations in attempts to clarify its role in METH-induced neurotoxicity. For example, ablation of nNOS-expressing interneurons in striatum does not protect against METH-induced TH or DAT depletions (Zhu et al., 2006; Fricks-Gleason and Keefe, 2013); however, there was incomplete mitigation of METH-induced NO production in such preparations (Fricks-Gleason and Keefe, 2013) raising questions as to whether the NO detected could be produced by constitutively expressed eNOS or result from diffusion away from residual nNOS-containing interneurons.

An alternative conclusion for the results of these studies is that NO is not sufficient for METH-induced neurotoxicity. To address this possibility, our lab utilized animals resistant to the acute neurotoxic consequences of METH exposure. In this model, animals were initially treated with METH or saline on PND60 and then allowed to recover for 30 days. At PND90, the rats were treated again with either METH or saline, resulting in four treatment groups based on PND60:PND90 treatment (Saline:Saline, Saline:METH, METH:Saline, and METH:METH). Under this paradigm, we and others have found that animals with partial DA loss induced by a neurotoxic regimen of METH fail to exhibit further decreases in striatal DA when re-exposed to METH at PND90 (Thomas and Kuhn, 2005; Hanson et al., 2009). Using this paradigm we were able to compare changes in NOS enzyme activity and protein nitration in animals experiencing acute toxicity when exposed to METH at PND90 (*i.e*. the saline:METH group) compared to animals not experiencing acute toxicity when exposed to METH at PND90 (*i.e*. the METH:METH group; (Friend et al., 2013). We found that both protein nitration and NOS activity were increased in both groups exposed to METH at PND90 (*i.e*. Saline:METH and METH:METH). Thus, NO was produced regardless of whether an animal was experiencing acute toxicity or not. These data, combined with data showing that METH exposure results in DA terminal damage in several brain regions (*i.e*. amygdala, hippocampus, and cortex) that do not exhibit changes in protein nitration (Anderson and Itzhak, 2006), indicate a significant dissociation between indices of NO production and acute DA neuron toxicity, suggesting that generation of NO is not sufficient for METH-induced DA toxicity.

Although NO does not appear to be sufficient for METH-induced DA nerve terminal degeneration, it may be necessary when toxicity does occur, as NO may act together with other factors under those conditions to contribute to the toxicity. Also, it is important to note that while this review has focused on the role, or lack thereof, of METH-induced NO production in DA nerve terminal degeneration, there remains the possibility that METH-induced NO production may contribute to METH-induced apoptosis of cells postsynaptic to DA nerve terminals. For example, ablation of nNOS-expressing interneurons in striatum prior to a bolus regimen of METH (1 injection of 30 mg/kg) protected against METH-induced cell death in striatum, but not DA depletions (Zhu et al., 2006; Wang et al., 2008; Zhu et al., 2009). Further, manipulations that decrease METH-induced protein nitriation also mitigate METH-induced striatal cell death (Zhang et al., 2013). Therefore, while METH-induced NO production may not be sufficient for METH-induced DA terminal degeneration, it may contribute to METH-induced striatal neuron apoptosis. Together, these data may suggest that mechanisms underlying METH-induced DA depletions differ from those underlying METH-induced striatal cell death, and thus studies examining the distinct

mechanisms mediating METH-induced DA terminal degeneration versus METH-induced apoptosis are needed.

Finally, given the significant glutamatergic and dopaminergic inputs to striatum, increased NO production during and following METH exposure may simply result from activity of these inputs. In fact, several studies have demonstrated how the projections to striatum influence the production of NO via nNOS. Both DA and glutamate (GLU) can regulate NO production via nNOS-expressing interneurons in striatum (Figure 1). Furthermore, the striatum receives extensive glutamatergic inputs from the cortex and the thalamus (Kemp and Powell, 1971; Kitai et al., 1976; Gerfen, 1989; Bellomo et al., 1998). The nNOS-expressing interneurons in striatum express NMDA-type GLU receptors (Gracy and Pickel, 1997), and intra-striatal infusion of NMDA receptor agonists (Iravani et al., 1998; Rossetti and Crespi, 2004) or application *in vitro* (Garthwaite et al., 1988; Bredt and Snyder, 1989) increases NO production. Furthermore, stimulation of corticostriatal afferents, both *in vitro* and *in vivo*, increases the production of NO via an nNOS-dependent mechanism (Kawaguchi, 1993; Sammut et al., 2007). In addition to GLU influencing NO production from nNOS-expressing interneurons, nNOS production can also be influenced by DA. For instance, the striatum also receives extensive dopaminergic inputs from the substantia nigra (Gerfen et al., 1987; Kubota et al., 1988; Vuillet et al., 1989), and nNOS-expressing neurons are known to express D1-type (D1 and D5) DA receptors (Le Moine et al., 1991; Rivera et al., 2002; Centonze et al., 2003). D1-type DA receptor or substantia nigra (Sammut et al., 2006) stimulation induces the production of NO (Le Moine et al., 1991; Sammut et al., 2006) and increases NADPH diaphorase staining in striatum (Morris et al., 1997; Hoque et al., 2010). Finally, NMDA and D1 DA receptor activation work together to increase NO production in striatum (Park and West, 2009). Therefore, these data, combined with studies demonstrating significant increases in both GLU (Nash and Yamamoto, 1992; Mark et al., 2004) and DA (O'Dell et al., 1991; Nash and Yamamoto, 1992; O'Dell et al., 1993) during and following exposure to a neurotoxic regimen of METH, suggest that NO produced by nNOS during METH exposure may simply be a readout of NMDA and DA receptor stimulation rather than a contributor to the neurotoxic process. Studies using specific manipulations of NMDA or DA receptors and then examining NO production during METH exposure would more directly address this possibility.

In conclusion, while a significant amount of data suggest that NO may play an important role in METH-induced DA terminal degeneration a growing amount of data also suggest that this NO production may not be sufficient for such neurotoxicity. Future work carefully manipulating the nitric oxide syanthases while controlling for METH-induced neurotoxicity will more clearly answer this question.

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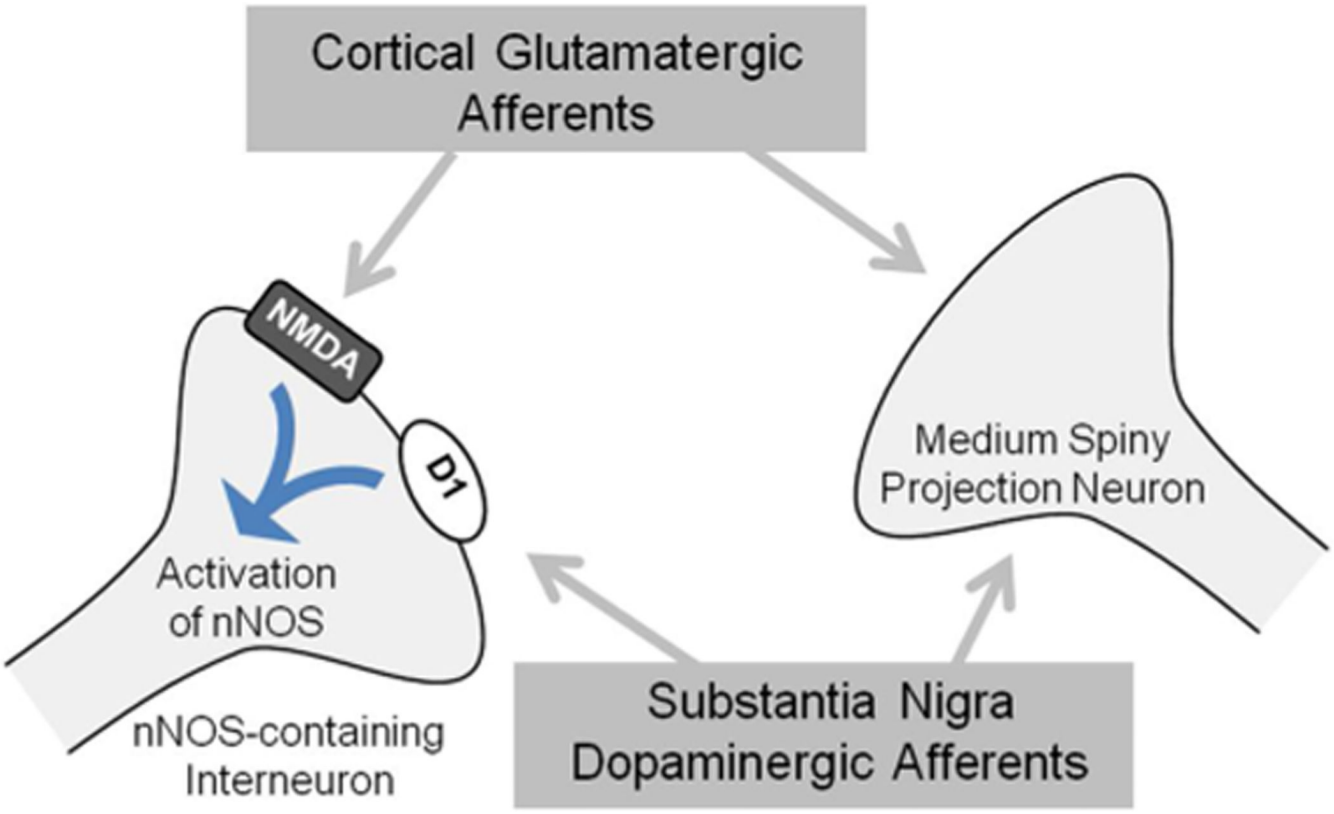

Figure 1.

Model of striatal nNOS regulation (adapted from West, 2010). nNOS-containing interneurons receive input from corticostriatal and nigralstriatal projections. nNOS-containing interneurons express both NMDA and D1 receptors. Stimulation of NMDA receptors activates nNOS to produce NO. In addition to corticostriatal activation of NMDA receptors, nigrostriatal DA inputs activate D1 receptors, increasing nNOS activity.