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Synergistic activity between the delta-opioid agonist SNC80 and amphetamine occurs *via* a glutamatergic NMDA-receptor dependent mechanism

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ABSTRACT

Glutamate is known to cause the release of dopamine through a Ca^{2+}-sensitive mechanism that involves activation of NMDA ionotropic glutamate receptors. In the current study, we tested the hypothesis that the delta opioid agonist SNC80 acts indirectly, *via* the glutamatergic system, to enhance both amphetamine-stimulated dopamine efflux from striatal preparations and amphetamine-stimulated locomotor activity. SNC80 increased extracellular glutamate content, which was accompanied by a concurrent decrease in GABA levels. Inhibition of NMDA signaling with the selective antagonist MK801 blocked the enhancement of both amphetamine-induced dopamine efflux and hyperlocomotion observed with SNC80 pretreatment. Addition of exogenous glutamate also potentiated amphetamine-stimulated dopamine efflux in a Mg^{2+}- and MK801-sensitive manner. After removal of Mg^{2+} to relieve the ion conductance inhibition of NMDA receptors, SNC80 both elicited dopamine release alone and produced a greater enhancement of amphetamine-evoked dopamine efflux. The action of SNC80 to enhance amphetamine-evoked dopamine efflux was mimicked by the $GABA_B$ antagonist 2-hydroxysaclofen. These cumulative findings suggest SNC80 modulates amphetamine-stimulated dopamine efflux through an intra-striatal mechanism involving inhibition of GABA transmission leading to the local release of glutamate followed by subsequent activation of NMDA receptors.

1. Introduction

Delta opioid receptor (DOR) agonists have many stimulant-like properties *in vivo*. For example, DOR agonists increase locomotor activity, produce conditioned place preference in rodents, and generalize to the discriminative effects of stimulants in rats and monkeys (Shippenberg et al., 1987; Longoni et al., 1998; Churchill and Kalivas, 1992; Suzuki et al., 1996, 1997; Longoni et al., 1998; Negus et al., 1998; Jutkiewicz et al., 2005). Despite these stimulant-like qualities, the nonpeptidic DOR agonist SNC80 is not self-administered by monkeys (Negus et al., 1998) and does not facilitate intracranial self-stimulation (Do Carmo et al., 2009). Consistent with these behavioral findings, SNC80 fails to promote dopamine efflux directly from rat striatum (Bosse et al., 2008) and does not increase extracellular dopamine levels in the caudate putamen or nucleus accumbens assessed by microdialysis following systemic administration (Longoni et al., 1998). Thus, SNC80 must modulate the dopaminergic system indirectly through other mechanisms or signaling pathways.

In addition to direct stimulant-like actions of DOR agonists there is considerable evidence that DOR activity can influence the actions of psychomotor stimulants in a variety of behavioral paradigms. For example, blocking DORs with the antagonist naltrindole (NTI) attenuates some of the behavioral effects of amphetamine and cocaine, suggesting that endogenous DOR receptor signaling may modulate stimulant activity (Jones and Holtzman, 1992; Menkens et al., 1992; Jones et al., 1993; Shippenberg and Heidbreder, 1995; Heidbreder et al., 1996). In addition, DOR activation with agonists such as SNC80 and TAN-67 can enhance the discriminative effects of

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stimulants in rats and monkeys (Suzuki et al., 1997; Negus et al., 1998; Rowlett and Spealman, 1998; Brandt et al., 1999), increase methamphetamine-induced injurious behavior (Mori et al., 2006), and significantly enhance amphetamine and cocaine-stimulated locomotor activity (Jutkiewicz et al., 2008). Consistent with these latter findings, DOR agonists augment amphetamine-stimulated dopamine release from rat striatal slices (Bosse et al., 2008). The mechanism(s) by which DOR activation with endogenous or exogenous ligands influences psychostimulant function is unknown.

Glutamate neurotransmission contributes to the expression of the stimulatory and reinforcing effects of psychostimulants (Kalivas, 2010). In rodents, antagonists selective for both ionotropic NMDA and non-NMDA glutamate receptors inhibit psychostimulant-mediated locomotor activity (Kelley and Throne, 1992; Willins et al., 1992; Pulvirenti et al., 1994), development of conditioned place-preference (Kaddis et al., 1995), and acquisition (Schenk et al., 1993) and rate of cocaine self-administration (Pulvirenti et al., 1992). Conversely, stimulation of ionotropic glutamate receptors augments the maintenance of cocaine self-administration and facilitates relapse to cocaine-seeking behavior (Cornish et al., 1999). Ultrastructural evidence demonstrates that cortical glutamate efferents make direct presynaptic associations with dopamine terminals in the rat striatum (Sesack and Pickel, 1990) and that ionotropic glutamate receptors are located on both nigrostriatal (Tarazi et al., 1998) and mesolimbic (Gracy and Pickel, 1996) dopaminergic nerve terminals. These data suggest glutamate modulates the behavioral effects of psychostimulants directly by altering dopamine overflow.

Evidence for interactions between DOR and glutamine systems has been shown, although findings differ across brain regions. In the rat striatum, high concentrations of the peptide DOR agonist DPDPE increase glutamate levels in dialysates (Billet et al., 2004); in support of this effect amphetamine-evoked glutamate release is decreased by DOR antagonism (Rawls and McGinty, 2000). In contrast, DOR agonists decrease glutamate release in the substantia nigra (Mabrouk et al., 2009) and, in morphine treated animals, in the central nucleus of the amygdala (Bie et al., 2009). Thus, we hypothesize that glutamatergic systems should play a central role in the neurobiological and stimulant-like behaviors of the non-peptidic DOR agonist SNC80. The goal of the present study was two-fold: 1) to investigate the effects of SNC80 on glutamate and GABA release in striatal slices and 2) to understand the role of glutamate in mediating the SNC80-induced enhancement of amphetamine-stimulated dopamine efflux and behaviors. Our results suggest that DOR activation by SNC80 indirectly enhances glutamate neurotransmission, most likely through GABA disinhibition in the striatum, to regulate amphetamine-induced behaviors and amphetamine-stimulated dopamine efflux primarily through activation of NMDA receptors.

2. Materials and methods

2.1. Animals

Male Sprague Dawley rats (250–350 g) were obtained from Harlan Sprague Dawley (Indianapolis, IN) and housed in groups of two or three animals. All animals were fed on a standard laboratory diet and kept on a 12 h light/dark cycle, with lights on at 6:30 A.M., at a temperature of 21 °C. Studies were performed in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the U.S. National Institutes of Health. The experimental protocols were approved by the University of Michigan Committee on the Use and Care of Animals. For these experiments, all efforts were made to reduce the number of animals and animal tissues used.

2.2. Drugs

SNC80 ((+)-4-[(α-R)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide), naltrindole hydrochloride (NTI), (+)MK801 ((5R,10S)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate), (+)BW373U86 ((+)-4-[(α(R)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl]-N,N-diethylbenzamide), and amphetamine sulfate were obtained from the Narcotic Drug and Opioid Peptide Basic Research Center at the University of Michigan (Ann Arbor, MI). L-glutamic acid was from Sigma (St. Louis, MO). 2-Hydroxysaclofen ((RS)-3-amino-2-(4-chlorophenyl)-2-hydroxy-propyl-sulfonic acid) was obtained from Tocris Biosceince (Bristol, UK). All compounds were dissolved in sterile water, except SNC80 which was dissolved in 0.08 M HCl. For the behavioral assays SNC80, (+)BW373U86, and amphetamine sulfate were administered by subcutaneous (s.c.) injection and MK801 was administered by intraperitoneal (i.p.) injection. For the dopamine release studies, drugs were diluted from stock solutions with Krebs-Ringer buffer (KRB) [125 mM NaCl, 2.7 mM KCl, 1.0 mM $MgCl_2$, 1.2 mM $CaCl_2$, 1.2 mM KH_2PO_4, 10 mM glucose, 24.9 mM $NaHCO_3$, and 0.25 mM ascorbic acid; oxygenated with 95% O_2/5% CO_2 for 1 h before use, with a final pH of 7.4].

2.3. Striatal tissue preparation

Rats were sacrificed by decapitation and the striatum, including both dorsal and ventral regions, was dissected from a coronal slice of the brain, chopped into approximately 1-mm^3 pieces, and divided for duplicate measures as described previously (Bosse et al., 2008). Wet tissue weight was measured in pre-weighed boats containing ice-cold KRB. Average wet weight (milligrams ± SEM) of the striatal slices was 35 ± 1.6 mg.

2.4. Dopamine release assay

Striatal tissue preparations from naïve rats were transferred onto Whatman GF/B glass-fiber filters (Maidstone, England) in the appropriate chambers of a Brandel superfusion apparatus (Brandel SF-12; Gaithersburg, MD). Superfusion chambers were maintained at 37 °C with KRB perfused through the chambers at a rate of 100 μl/min. The perfusates were collected in 5 min fractions into vials containing 25 μl internal standard solution (0.05 M $HClO_4$, 4.55 mM dihydroxybenzylamine (DHBA), 1 M metabisulfate, and 0.1 M EDTA). Unless otherwise stated striatal preparations were perfused with KRB alone or KRB containing, SNC80 (10 μM) or glutamic acid (0.1, 1, 10, 100 mM) for 30 min (fractions 1–6) after which KRB containing amphetamine sulfate (100 μM) was perfused through the preparations during the 5 min collection of fraction 7. The amphetamine-containing buffer was then replaced with fresh KRB and fraction collection was continued for an additional 40 min (fractions 8–15). Administration of either SNC80 or glutamate was discontinued during the addition of amphetamine and subsequent perfusates. In experiments employing the NMDA antagonist, (+)MK801 (10 μM) was perfused 20 min prior to the start of fraction collection and continued throughout the experiment. For experiments with the $GABA_B$ antagonist 2-hydroxysaclofen, after 2 fractions of basal perfusate were collected 2-hydroxysaclofen (10 μM) or SNC80 (10 μM) for comparison was perfused for 30 min (fractions 3–8) after which a new KRB solution containing amphetamine (100 μM; fraction 9 only) was perfused through the preparation for 5 min. Results were not corrected for the time taken for drug to reach the striatal preparations.

Fractions were stored at −80 °C and measured within a month for dopamine content by HPLC with electrochemical detection (EC) or, for the experiments with the $GABA_B$ antagonist, by HPLC coupled with mass spectrometry (MS). Samples were filtered through 0.22 μm PVDF syringe filters (Whatman; Florham Park, NJ) before analysis. For HPLC-EC detection 50 μl of each sample was injected on a Symmetry reverse phase C-18 3.5 μm column coupled to a Waters HPLC system, which employed an isocratic pump (Waters 1515) and an electrochemical detector (Waters 2465). The electrochemical detector used a glassy carbon electrode with a potential of +0.6 V against an Ag/AgCl reference electrode and the sensitivity was set at 200 pA/V. Mobile phase (60 mM NaH_2PO_4, 30 mM citric acid, 0.1 mM EDTA, 0.021 mM sodium dodecyl sulfate, and 2 mM NaCl in 25% methanol/75% HPLC-grade water, apparent pH of 3.3) was pumped at a rate of 0.8 ml/min. The chromatograms resulting from sample runs were analyzed for peak area using Breeze software (Waters; Milford, MA). Dopamine content in pmol/mg wet weight was standardized based on the relative ratio of the peak area of dopamine to the peak area of the internal standard DHBA in each individual fraction relative to the standard curve. Standards of known concentrations of dopamine were prepared in KRB and a 6 point concentration standard curve was obtained for each assay. The standard curve for dopamine was linear from 12.5 to 2500 pg.

For HPLC-MS detection of dopamine, samples were derivatized by benzoylation as previously described (Song et al., 2012). Briefly, to 10 μl samples was added 5 μl of 100 mM borate buffer, 2% benzoyl chloride in acetonitrile, and C-13 benzoyl chloride-derivatized internal standards. Samples were injected automatically using a Waters (Milford, MA) nanoAcquity ultra HPLC with a TSS H3 column (1 mm × 100 mm) coupled to an Agilent 6410 (Agilent Technlogies, Santa Clara, CA) triple quadrupole mass spectrometer for analysis. This system is highly sensitive for measurements of dopamine, down to the picomolar levels (Song et al., 2012).

2.5. Glutamate and GABA release assay

Striatal tissue was prepared and perfused as described under the dopamine release assay. Samples were collected for the measurement of both glutamate and GABA levels during a 25 min perfusion with either KRB alone or KRB containing SNC80 (10 μM) (fractions 4–8). For antagonist studies, naltrindole (10 nM) was perfused for 30 min prior to and during SNC80. Fractions were collected in vials containing 1 M adipic acid (in 55 μl 0.05 M $HClO_4$, 4.55 mM 1 M metabisulfate, and 0.1 M EDTA) as internal standard.

Samples were analyzed off-line simultaneously for both glutamate and GABA content using a home-built capillary electrophoresis instrument with laser-induced fluorescence detection as described by Bowser and Kennedy (2001). A CMA 11 microdialysis probe (CMAMicrodialysis, Harvard Apparatus, Holliston, MA) was lowered into each perfusate sample (heated to 37.4 °C in a water bath) until the 4 mm sampling area was immersed. The microdialysis probe was perfused with artificial cerebrospinal fluid (145 mM NaCl, 2.68 mM KCl, 1.01 mM $MgSO_4$, 1.22 mM $CaCL_2$, 1.55 mM Na_2HPO_4, and 0.45 mM NaH_2PO_4 (pH 7.4)) at a flow rate of 1.0 μl/min. Dialysate was collected and mixed with 10 mM *ortho*-phthaldialdehyde, in a buffer of 40 mM β-mecaptoethanol, 36 mM sodium tetraborate decahydrate, 0.81 mM 2-Hydroxypropyl-β-cyclodextrin and 10 mM EGTA in 10% methanol) to derivatize primary amines. Samples were then loaded onto the separation capillary (9.5 cm, 10 μm internal diameter) *via* electrokinetic injection. A voltage of −20 kV was applied to separate the dialysate sample. Laser-induced fluorescence was collected inside a sheath flow cuvette containing 40 mM sodium tetraborate decahydrate (pH 10.0) using the 351 nm line from an Argon Ion laser (Coherent, Santa Clara, CA). Fluorescence at 450 nm was collected orthogonally using a photomultiplier tube. Electropherograms were collected and analyzed using programs written in LabView (National Instruments, Austin, TX).

2.6. Locomotor activity

Locomotor activity was measured by implanting singly-housed rats with telemetry devices (model ER-4000 E-Mitter, Mini Mitter Co., Bend, OR). Under anesthesia with ketamine (90 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) the abdomen was cleaned with betadine and alcohol then a 1–2 cm rostral-caudal incision was made to expose the peritoneal cavity. The radiotransmitter was placed inside the peritoneal cavity and the incision closed with absorbable gastro-intestinal 4-0 coated vicryl suture. Implant surgeries were conducted at least 6 days prior to measuring locomotor activity. The implanted transmitters produced activity signals that were sent to a receiver (model ER-4000 Receiver, Mini Mitter Co.) placed directly under the home cage of each rat. Home cages were placed on the receivers at least 15 h prior to an experiment. Baseline locomotor activity was collected for at least 40 min prior to the first drug injection (time 0) without disturbing the home cage. Rats (n = 5–8) were administered MK801 (0.1 mg/kg, i.p.) 30 min prior to either amphetamine sulfate (1.0 mg/kg, s.c.) or SNC*80* (10.0 mg/kg, s.c.) (Fig. 6a). SNC80 was administered at time 0 followed 150 min later by MK801, followed 30 min later by amphetamine (Fig. 6b). Data were collected and processed simultaneously by the Vital View data acquisition system (Mini Mitter Co.).

2.7. Data and statistical analyses

Data for dopamine release experiments are presented as mean values of striatal tissue from four rats, each run in duplicate. Release of dopamine was graphed as the amount of endogenous dopamine in pmol/mg wet weight of tissue collected in each fraction. In experiments using mass spectrometry for detection of neurochemicals, dopamine, glutamate and GABA data are expressed as percent of efflux relative to basal levels (prior to the addition of drug). In some figures, dopamine release curves are presented as area under curve (AUC) generated from GraphPad Prism 4 software using the trapezoidal method. The AUC was computed from the individual dopamine release curves plotted as the cumulative measurement of dopamine efflux after subtracting each baseline (0.33 ± 0.02 pmol/mg wet weight). Behavioral experiments were performed with 5–8 rats for each group.

Statistical significance was assessed using either Student's t-test or repeated measured analysis of variance (ANOVA) with the appropriate post-hoc tests (Pairwise multiple comparison procedures (Tukey's test) or Bonferroni multiple comparison assessment) as noted in the figure legends. Data were analyzed using either GraphPad Prism 4 software (San Diego, CA) or Systat Sigma Stat 3.5 (San Jose, CA). In some instances, if a significant interaction is reported, the main effects were also significant but are not always reported. Differences were considered significant if $p < 0.05$.

3. Results

3.1. SNC80 elicits opposite effects on the release of endogenous glutamate and GABA from rat striatal slices

This experiment aimed to determine if SNC80 altered extracellular glutamate and GABA levels in perfused rat striatal slices. SNC80 (10 μM) increased glutamate efflux as compared with basal control (Fig. 1a). There were significant main effects of SNC80 treatment ($F(2,143) = 19.66$, $p < 0.0001$) and fraction ($F(5,143) = 5.85$, $p < 0.0001$), but there was no significant interaction. Analysis of the significant main effects demonstrated that perfusion of naïve rat striatal preparations with 10 μM SNC80 evoked a rapid, increase in basal endogenous glutamate levels compared with control, specifically at fractions 4 ($p < 0.001$), 5 ($p < 0.01$), and 6 ($p < 0.01$). However, the effect returned to baseline after 20 min (fraction 7) even in the continued presence of SNC80. The selective DOR antagonist naltrindole (NTI; 10 nM) significantly attenuated the SNC80-mediated release of glutamate at fractions 4 ($p < 0.01$) and 5 ($p < 0.05$) and did not differ from basal at any fraction.

Treatment with SNC80 also altered GABA efflux measured simultaneously from the same tissue perfusates used to assess glutamate content (Fig. 1b) with significant main effects for SNC80 treatment ($F(2,143) = 9.0$, $p = 0.0002$) and fraction ($F(5,143) = 6.3$, $p < 0.0001$), but no significant interaction. Perfusion of naïve rat striatal preparations with 10 μM SNC80 evoked a rapid, but

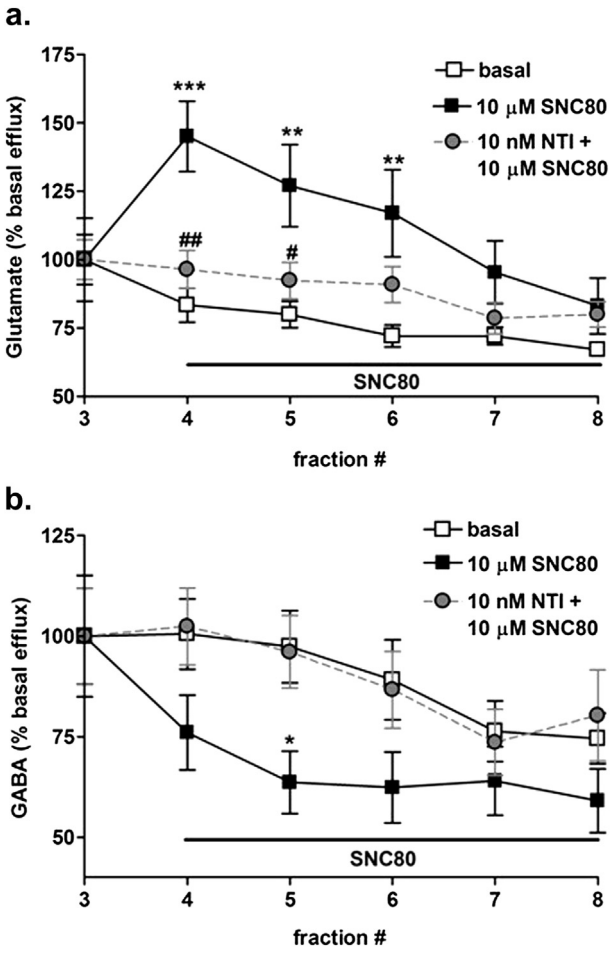

Fig. 1. SNC80 modulates the endogenous release of a) glutamate and b) GABA from rat striatal preparations. Baseline samples were collected for 15 min (fractions 1–3) from naïve rat striatal tissue before perfusion with 10 μM SNC80 for 25 min (fraction 4–8). The selective delta antagonist, NTI (10 nM), was perfused for 30 min prior to and throughout treatment with SNC80. Fractions were simultaneously measured by capillary electrophoresis for both glutamate and GABA content as described in the Materials and methods. Data were graphed as percent of basal efflux pmol/mg wet weight (±S.E.M.) for both glutamate (6.38 ± 0.60) and GABA (3.99 ± 0.25) (n = 4 in duplicate). Statistical significance was determined by two-way ANOVA with Tukey's post-hoc test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared to basal; #$p < 0.05$, ##$p < 0.01$ compared to SNC80 alone.

transient, decrease in basal endogenous GABA release compared with control that was statistically significant at fraction 5 only ($p < 0.05$). The SNC80-induced decrease in GABA was attenuated by pretreatment with NTI to levels that were not different from control.

3.2. Exogenously added glutamate promotes dopamine release alone and potentiates amphetamine-stimulated dopamine efflux from rat striatal tissue

Since we hypothesized that the increased release of glutamate in response to SNC80 is responsible for the SNC80-mediated enhancement of amphetamine-stimulated dopamine efflux, we next examined the effect of exogenous glutamate. A 30 min perfusion with L-glutamic acid produced a concentration-dependent increase in dopamine efflux (Fig. 2a, clear bars; $F(2,16) = 79.5$, $p < 0.0001$). After removal of Mg^{2+} from the buffer to relieve block of NMDA receptors (Crunelli and Mayer, 1984, Fig. 2a, hatched bars) the glutamate-induced increase in dopamine release ($F(2,15) = 48.1$, $p < 0.0001$) was significantly enhanced ($F(1,17) = 213$) at both 1 mM ($p < 0.05$) and 10 mM ($p < 0.01$) glutamic acid. The glutamic acid-induced (10 mM) dopamine efflux was attenuated by the NMDA antagonist MK801 (Fig. 2b; $p = 0.003$) and by removal of Ca^{2+} ions from the perfusion buffer (Fig. 2c; $p = 0.0004$).

To confirm that glutamate acting at NMDA receptors can amplify amphetamine-stimulated dopamine efflux, naïve striatal slices were perfused with or without glutamic acid for 30 min. Glutamic acid pretreatment (10 mM) increased amphetamine-stimulated dopamine efflux (Fig. 3a) as compared with no pretreatment (main effects for glutamic acid pretreatment ($F(1,22) = 100.2$, $p < 0.0001$), but no significant interaction). The combined effects of amphetamine plus glutamate were significantly greater than the predicted additive effects ($p = 0.0006$), indicating that the effect is synergistic. The NMDA antagonist MK801 blocked glutamic acid-induced augmentation of amphetamine-stimulated dopamine efflux ($F(1,22) = 49.2$, $p < 0.0001$), but did not significantly alter dopamine efflux stimulated by amphetamine alone (Fig. 3b). Similarly, removal of extracellular Ca^{2+} attenuated the increase in amphetamine-stimulated dopamine efflux induced by pretreatment with L-glutamic acid ($F(1,25) = 32.3$, $p < 0.0001$), but had no effect on amphetamine-stimulated dopamine efflux alone (Fig. 3b).

3.3. Enhancement of amphetamine-stimulated dopamine efflux with SNC80 treatment is altered by removal of extracellular Mg^{2+} and by selective antagonism of NMDA receptors with MK801

A previous study demonstrated that SNC80 dose-dependently augmented amphetamine-stimulated dopamine efflux in the striatum (Bosse et al., 2008). Considering that SNC80 stimulated glutamate efflux in the striatum and L-glutamic acid enhanced amphetamine-stimulated dopamine release, the next experiments evaluated whether glutamate signaling contributed to SNC80-mediated enhancement of amphetamine-stimulated dopamine efflux.

Dopamine efflux levels following vehicle perfusion were not altered in Mg^{2+}-free conditions at basal (Fig. 4; fractions 1–6) or after amphetamine exposure (Fig. 4; fractions 8–14). However, removal of Mg^{2+} from the perfusion buffer significantly altered the effects of SN80 alone and the effects of SNC80 pretreatment on amphetamine-stimulated dopamine efflux (Fig. 4; SNC80 pretreatment × Mg^{2+} × fraction interaction: $F(14,479) = 3.43$, $p < 0.0001$). Removal of Mg^{2+} revealed an ability of SNC80 alone to release dopamine, although this effect was small and only significant at fraction 1 ($p < 0.0001$). In the presence of Mg^{2+}, SNC80 pretreatment enhanced amphetamine-induced dopamine efflux above vehicle pretreatment at fractions 10 and 11 ($p < 0.0001$) and this effect was markedly enhanced in the absence of Mg^{2+} at fractions 9–14 ($p < 0.0001$).

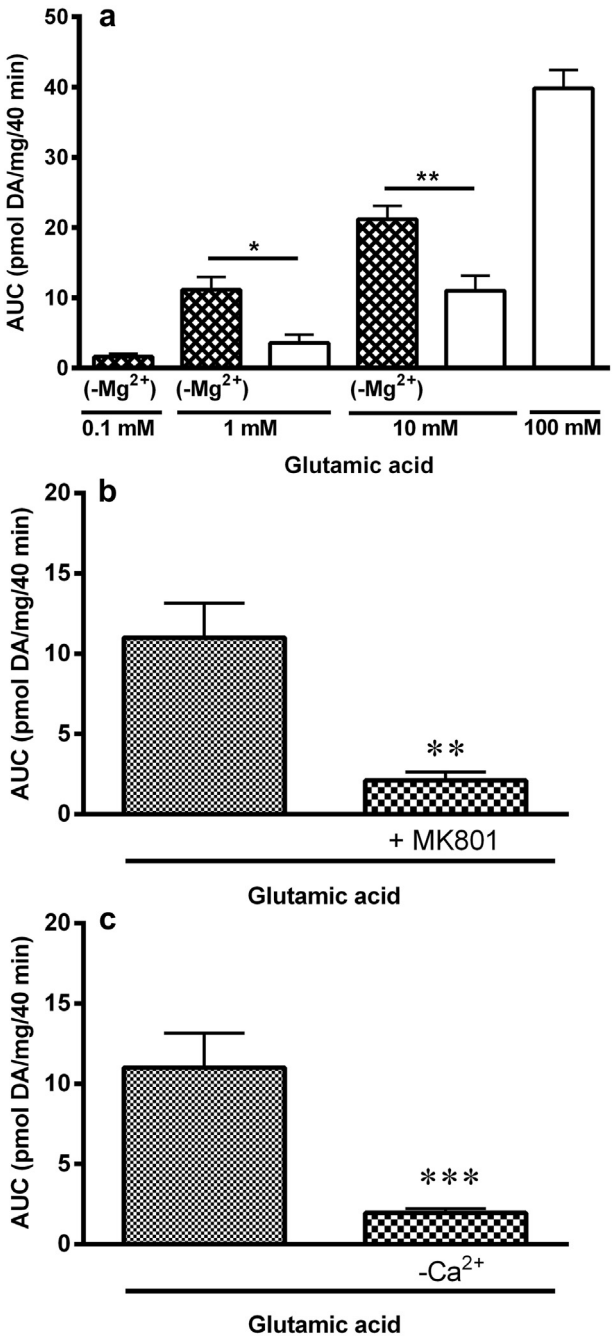

Fig. 2. Exogenously added L-glutamic acid induces dopamine efflux in a (a) Mg^{2+}, (b) MK801 and (c) Ca^{2+}-sensitive manner. Dopamine (DA) content of the fractions was measured by HPLC with electrochemical detection as described in the Materials and methods and plotted as AUC (pmol DA/mg (wet weight)/40 min) (±S.E.M.) obtained from the time versus release curves of each treatment group ($n = 4$ in duplicate). (a) Rat striatal preparations were perfused with 0.1–100 mM L-glutamic acid for 30 min in either the presence (open bars) or absence (hatched bars) of Mg^{2+} in the perfusion buffer. The concentration-dependent L-glutamic acid-induced increase in dopamine release was significant in both the presence and absence of Mg^{2+}. Removal of Mg^{2+} augmented the effects of L-glutamic acid on dopamine release at 1 and 10 mM L-glutamic acid, $^{*}p < 0.05$, $^{**}p < 0.01$ respectively, by two-way ANOVA with Bonferroni post-hoc test. (b) MK801 (10 μM) or (b) Ca^{2+} removal from the buffer also significantly decreased glutamic acid-induced dopamine release. $^{**}p < 0.01$ and $^{***}p < 0.001$ compared with control by Student's *t*-test.

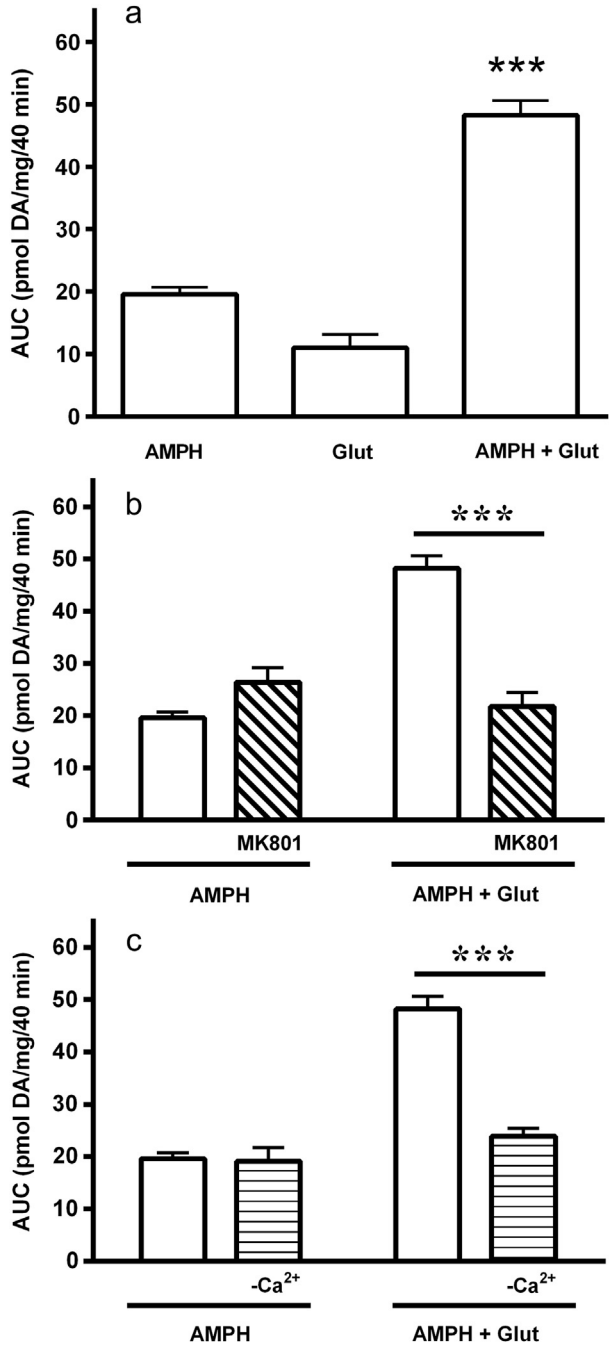

Fig. 3. Dopamine efflux from rat striatal slices elicited by amphetamine with or without L-glutamic acid pretreatment. Striatal slices were perfused with vehicle or 10 mM L-glutamic acid for 25 min then perfused with 100 μM amphetamine for 5 min and perfusates were collected for 30 min. Dopamine (DA) content of the fractions was measured as described in Fig. 2 and plotted as AUC (pmol DA/mg (wet weight)/40 min) (±S.E.M.). a) Pre-treatment with 10 mM L-glutamic acid for 30 min synergistically enhanced amphetamine-induced (100 μM) dopamine efflux ($p = 0.0006$ by Student's *t*-test compared to the theoretical additive effects of glutamate and amphetamine). b) This effect was significantly attenuated by MK801 ($p < 0.001$) and (c) Ca^{2+} removal ($p < 0.001$), assessed by two-way ANOVA with Bonferroni post-hoc test.

The next experiments evaluated whether the NMDA receptor antagonist MK801 altered dopamine efflux with SNC80 pretreatment alone and following amphetamine exposure. During SNC80 pretreatment alone (Fig. 5a), there was a significant interaction ($F(1,20) = 19.6$, $p = 0.0003$). SNC80 alone increased dopamine efflux only in the absence of Mg^{2+} ($p < 0.001$) as previously

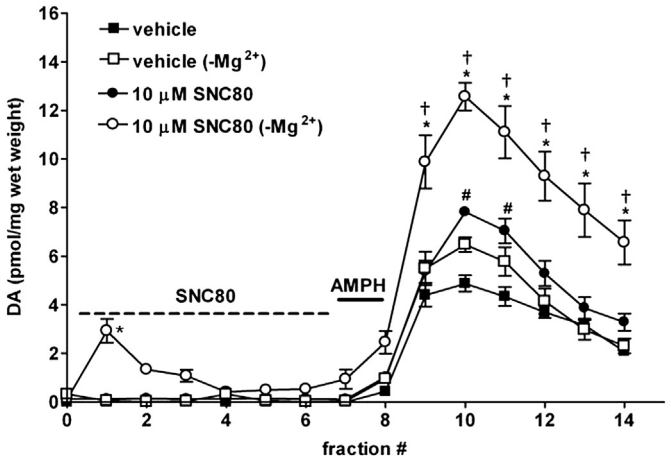

Fig. 4. Effect of the DOR agonist SNC80 on amphetamine-mediated dopamine efflux from striatal tissue in the presence and absence of Mg^{2+}. Striatal preparations from naïve rats were treated with 10 μM SNC80 30 min prior to a 5 min perfusion with 100 μM amphetamine, in the presence or absence of Mg^{2+}. Fractions were collected at 5 min intervals for an additional 40 min. Data are graphed as pmol of dopamine/mg wet weight (±S.E.M) ($n = 4$ in duplicate). Statistical significance was determined by $2 \times 2 \times 14$ ANOVA with Tukey's post hoc test. #$p < 0.0001$ compared to vehicle pretreatment with Mg^{2+}; *$p < 0.0001$ compared to vehicle without Mg^{2+}; †$p < 0.001$ compared to SNC80 with Mg^{2+}.

demonstrated (Fig. 4), that was reversed by MK801 back to baseline values ($p < 0.0001$; Fig. 5a). MK801 alone did not alter basal dopamine efflux. During and following the amphetamine exposure (Fig. 5b), SNC80 enhanced amphetamine-stimulated dopamine efflux as compared with vehicle pretreatment (Fig. 5b; significant interaction: $F(3,44) = 5.25$, $p = 0.004$) in both the presence and absence of Mg^{2+} as demonstrated by post hoc analyses (one-way ANOVA with Tukey's post hoc test: Mg^{2+}-containing buffer ($F(3,24) = 5.13$, $p = 0.008$) and Mg^{2+}-free buffer ($F(3,29) = 18.8$, $p < 0.0001$), and this enhancement was greater in Mg^{2+}-free buffer as compared with control buffer as previously observed (Fig. 5a and b; $p < 0.0001$ by post hoc analysis from two-way ANOVA). MK801 attenuated the effects of SNC80 pretreatment on amphetamine-stimulated dopamine efflux in the presence ($p < 0.05$) and absence of Mg^{2+} ($p < 0.001$) such that DA efflux levels did not differ from control (Fig. 5b); MK801 alone did not alter amphetamine-stimulated dopamine efflux.

3.4. The NMDA selective antagonist MK801 attenuates the SNC80-induced enhancement of amphetamine-stimulated locomotor activity

To parallel the above *in vitro* experiments, we evaluated the role of the NMDA receptor in SNC80-induced potentiation of amphetamine-stimulated activity. As previously demonstrated (Jutkiewicz et al., 2008), administration of either SNC80 (10 mg/kg, s.c.) or amphetamine (1.0 mg/kg, s.c.) alone produced increases in locomotor activity in rats, while 3 h pretreatment with SNC80 enhanced the locomotor-stimulating effects of amphetamine. Pretreatment with MK801 at a dose of 0.1 mg/kg, (i.p.) had no effect on the total locomotor activity counts stimulated by either amphetamine or SNC80 alone (Fig. 6a). However, when this dose of MK801 was administered after SNC80 and 30 min prior to amphetamine challenge (Fig. 6b), the potentiation of amphetamine-induced locomotor activity mediated by SNC80 was abolished ($F(68,272) = 1.73$, $p < 0.01$) and returned locomotor activity to levels observed with amphetamine alone ($p > 0.05$).

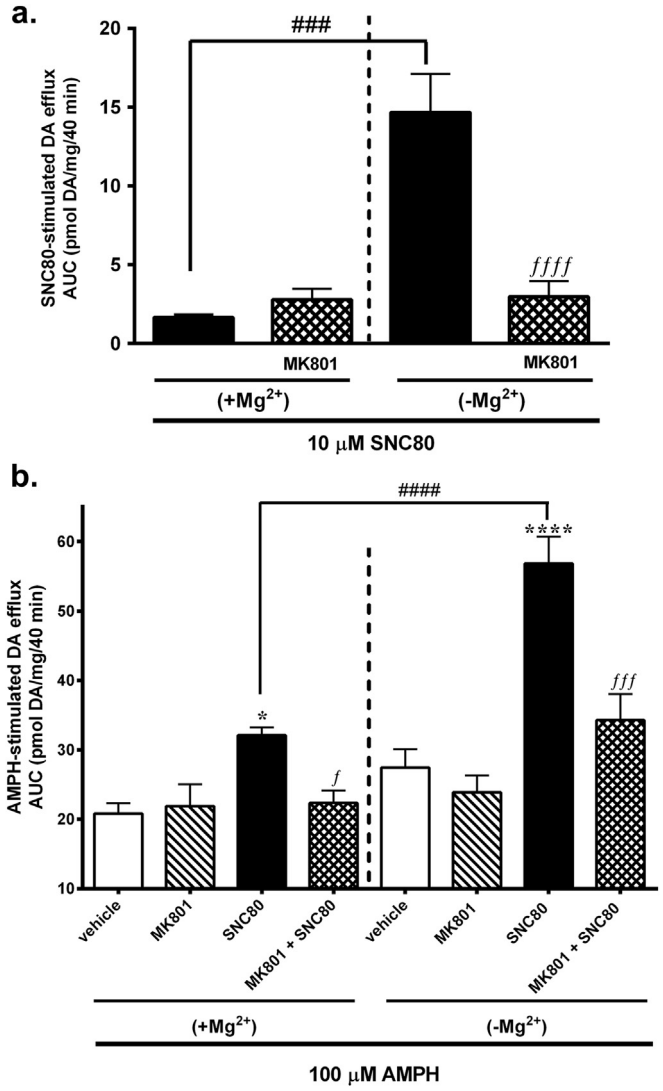

Fig. 5. The NMDA selective antagonist MK801 attenuates a) dopamine release induced by SNC80 alone in Mg^{2+}-free buffer and b) SNC80-induced modulation of amphetamine-mediated dopamine efflux in either standard or Mg^{2+}-free buffer. Striatal preparations were perfused for 20 min with 10 μM MK801 prior to and during treatment with buffer containing10 μM SNC80 for 30 min, followed by 100 μM amphetamine sulfate for 5 min. Samples were collected at 5 min intervals for an additional 40 min, during which perfusion with MK801 was continued. Dopamine (DA) content of the fractions was measured as described in Fig. 2 and plotted as AUC (pmol DA/mg (wet weight)/40 min) (±S.E.M.). Statistical significance was determined in a) by two-way ANOVA with Tukey's post hoc test and b) by two-way ANOVA followed by Tukey's post hoc test and one-way ANOVAs as post hoc tests for analyses within each Mg^{2+} condition. $^{*}p < 0.05$ and $^{****}p < 0.0001$ as compared with vehicle control in each Mg^{2+} condition, $\#\#\#p < 0.001$ and $\#\#\#\#p < 0.0001$ as compared with treatment in other Mg^{2+} condition, $fp < 0.05$, $fffp < 0.001$ and $ffffp < 0.0001$ as compared with SNC80 alone within each Mg^{2+} condition.

3.5. The $GABA_B$ antagonist 2-hydroxysaclofen enhances amphetamine-stimulated dopamine efflux in rat striatal tissue

We next sought to further probe the mechanism by which SNC80 enhances amphetamine-stimulated dopamine efflux. Considering the majority of DORs are located on inhibitory GABA terminals, we hypothesized that DOR activation inhibits GABA release, thus disinhibiting glutamate efflux to ultimately promote amphetamine-stimulated dopamine release. To evaluate this hypothesis, we determined whether attenuating GABA receptor signaling thereby mimicking the proposed effects of SNC80 would

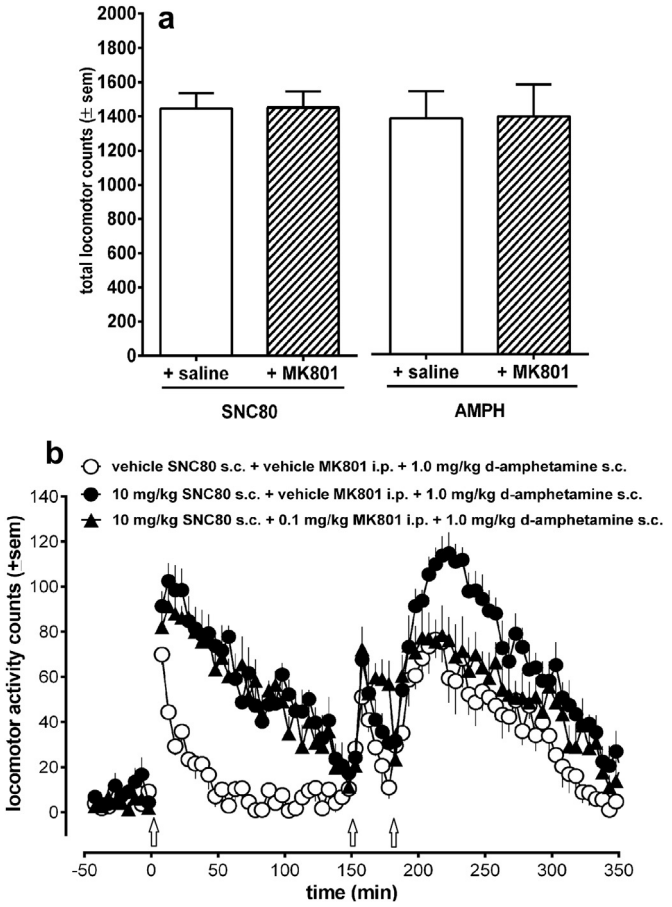

Fig. 6. Effect of antagonism of NMDA receptors by MK801 on locomotor stimulation elicited upon a) treatment with either SNC80 or amphetamine alone or b) amphetamine following SNC80. Male Sprague-Dawley rats (5–8 per group) were injected with: a) 0.1 mg/kg MK801 (i.p.) 30 min prior to either 10 mg/kg SNC80 (s.c.) or 1.0 mg/kg amphetamine (AMPH; s.c.) or b) 10 mg/kg SNC80 (arrow at time 0) 2.5 h prior to 0.1 mg/kg MK801 (arrow at150 min) followed 30 min later by 1.0 mg/kg amphetamine (arrow at 180 min). Data are plotted in a) as total locomotor counts (±S.E.M.) and in b) as mean locomotor counts summed every 5 min over time. Statistical significance was determined in a) by Student's *t*-test and in b) by two-way ANOVA with Tukey's post-hoc test.

enhance amphetamine-stimulated dopamine efflux in striatal slices. Perfusion with the $GABA_B$ receptor antagonist 2-hydroxysaclofen for 30 min increased amphetamine-stimulated dopamine release as compared with vehicle control ($F(2,13) = 6.1$, $p = 0.01$; Fig. 7). Both SNC80 and 2-hydroxysaclofen significantly increased amphetamine-stimulated dopamine efflux over vehicle control ($p < 0.05$) and to a similar extent.

4. Discussion

In this work we propose that the observed synergistic actions of SNC80 and amphetamines (Mori et al., 2006; Jutkiewicz et al., 2008; Bosse et al., 2008) and other possible stimulant-like properties of SNC80 (Suzuki et al., 1997; Negus et al., 1998; Rowlett and Spealman, 1998; Brandt et al., 1999), involves a glutamatergic mechanism. Firstly, SNC80 dually promoted glutamate release and decreased GABA release from striatal tissue. Secondly, the effects of SNC80 alone on dopamine release and the synergistic effect of SNC80 and amphetamine were sensitive to Mg^{2+} ions. Both of these effects and the synergistic effect on behavior, were blocked by MK801, implicating NMDA glutamatergic receptors; MK801 did not alter dopamine efflux in response to amphetamine alone,

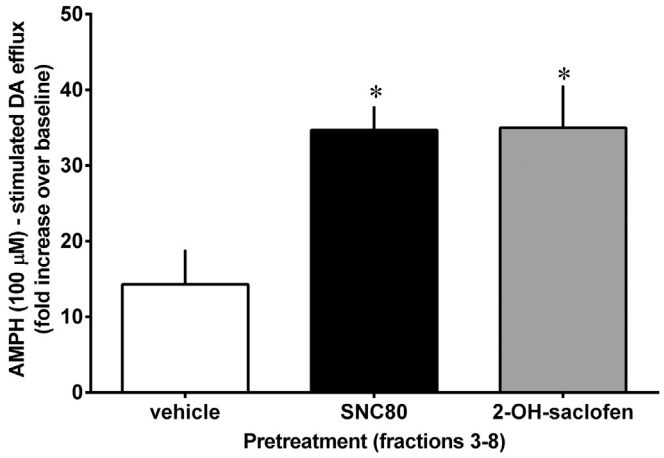

Fig. 7. Effect of $GABA_B$ receptor antagonism by 2-hydroxysaclofen on amphetamine-mediated dopamine efflux from rat striatal tissue. Striatal preparations were perfused with vehicle, 10 μM SNC80, or 10 μM 2-hydroxysaclofen for 30 min, then perfused with 100 μM amphetamine for 5 min and perfusates were collected for 25 min. Dopamine (DA) content was measured as described in Fig. 2 and plotted as fold increase over baseline (pmol DA/mg wet tissue weight) (±S.E.M.). Statistical significance was determined by one-way ANOVA followed by Bonferroni's post hoc test. $^*p < 0.05$ compared with vehicle.

confirming signaling through NMDA receptors is required for the SNC80-mediated enhancement. Also, L-glutamic acid added exogenously to striatal preparations mimicked the effects of SNC80 pretreatment on amphetamine-stimulated dopamine release in a MK801-sensitive manner. Finally, the $GABA_B$ antagonist saclofen reproduced the effect of SNC80 on amphetamine-mediated dopamine release. Considering the majority of DORs are located on GABAergic terminals (Svingos et al., 1998), together these data suggest that the primary activity of SNC80 is to inhibit GABA release thereby leading to a disinhibition of glutamate efflux, allowing glutamate to act on NMDA receptors that are known to be located on dopaminergic nerve terminals (Krebs et al., 1991). However, a mechanism by which SNC80 also decreases GABA release directly to enhance dopamine release or to contribute to enhanced dopamine release in this model cannot be ruled out. A schematic of the proposed mechanism is provided in Fig. 8.

SNC80 rapidly induced an approximate 40% increase in the levels of glutamate released from perfused striatal tissue as compared with vehicle; this effect relied on activation of DOR, as it was reversed by the selective antagonist NTI. A microdialysis study by Billet et al. (2004) has previously demonstrated that direct infusion of the peptide DPDPE into rat striatum can induce glutamate efflux. Previous work demonstrated that a small portion of DORs are located on presynaptic excitatory terminals (Svingos et al., 1998; Billet et al., 2004) and terminals of corticostriatal neurons (Billet et al., 2012). However, most DORs are associated with inhibitory synapses (Svingos et al., 1998) and work with synaptosomal preparations does not support the existence of DOR on striatal glutamate terminals (Rawls and McGinty, 1999). Certainly, the role of DOR agonists in directly enhancing glutamate release seems unlikely given that opioid receptors couple to inhibitory G-proteins thereby typically inhibiting neurotransmitter release and reducing neuronal excitability (Jiang and North, 1992). Indeed, DOR agonists decrease glutamate release *in vitro* (Ueda et al., 1995; Vlaskovska et al., 1997) and systemic SNC80 reduces glutamate release in the rat substantia nigra (Mabrouk et al., 2008). These reports suggests striatal DORs increase glutamine release in the striatum by an indirect mechanism.

Our finding that SNC80 inhibits GABA release in striatal slices, suggests a mechanism whereby DOR receptor agonists stimulate glutamate release, probably from cortical glutamatergic efferent neuronal terminals, *via* inhibition of GABA release from striatal interneurons. In support of this, attenuating GABA signaling by blockade of $GABA_B$ receptors in striatal slices also increased amphetamine-stimulated dopamine release to a similar extent produced by SNC80 perfusion. DORs have been identified on inhibitory terminals in the nucleus accumbens (Svingos et al., 1998), which are primarily GABAergic interneurons that contain opioid peptides (Oertel et al., 1983) and are capable of locally modulating striatal dopamine transmission (Smolders et al., 1995). Additionally, there is evidence for synaptic associations between neurons containing opioid peptides and cortical glutamatergic neurons from the cortex, which converge on common recipient neurons (Bouyer et al., 1984). Together, these data support an indirect mechanism by which DOR activation increases glutamate efflux to potentiate amphetamine-stimulated dopamine efflux in striatal slices, as depicted in Fig. 8.

Supporting the idea that the synergistic action of SNC80 involves promotion of glutamate efflux and activation of NMDA receptors, exogenous addition of glutamic acid directly elicited dopamine overflow from rat striatal preparations in a concentration-dependent, Mg^{2+}-dependent, and MK801-sensitive manner. Furthermore, perfusion of glutamic acid directly to striatal preparations, at concentrations which had little effect on dopamine overflow alone, synergistically enhanced amphetamine-evoked dopamine efflux though an NMDA receptor-dependent mechanism. The role of glutamate signaling through NMDA receptors in the SNC80 enhancement of amphetamine-stimulated dopamine efflux was confirmed because the effect of SNC80 was modulated by Mg^{2+}, which prevents NMDA elicited responses (Crunelli and Mayer, 1984) and blocked with the NMDA selective antagonist MK801. Furthermore, the involvement of glutamatergic transmission was supported by behavioral studies. A low dose (0.1 mg/kg) of MK801 produced no effect on SNC80- or amphetamine-stimulated locomotor activity alone, which coincides with a previous report (Druhan et al., 1996); however, MK801 abolished the enhancement of amphetamine-stimulated locomotor activity produced by SNC80 pretreatment. These overall findings identify a role for NMDA receptors in the behavioral and neurochemical interaction between DOR agonists and amphetamines. This model is in line with previous *in vivo* (Moghaddam et al., 1990) and *in vitro* (Roberts and Anderson, 1979; Wang, 1991) studies demonstrating that glutamate exerts, through activation of NMDA receptors, a presynaptic, faciliatory influence on dopamine release in rat striatum.

Previous studies have shown that systemic administration of SNC80 alone does not induce dopamine efflux from either the caudate putamen or nucleus accumbens measured by *in vivo* microdialysis (Longoni et al. (1998) or from striatal slice preparations (Bosse et al., 2008), even though SNC80 synergistically enhanced dopamine efflux in response to amphetamine (Bosse et al., 2008). The reason why SNC80 induces glutamate release but not the release of dopamine is not immediately clear given that SNC80 is more selective and more efficacious than DPDPE (Jutkiewicz et al., 2005) which has been demonstrated to promote dopamine overflow *in vivo* after i.c.v. (Spanagel et al., 1990) or intrastriatal (Dourmap and Costentin, 1994; Billet et al., 2004) administration. However, in our striatal slice preparation DPDPE, like SNC80, did not cause dopamine release (Bosse et al., 2008), suggesting this is not a difference between small molecule versus peptidic DOR agonists. In the absence of Mg^{2+}, SNC80 alone did release a small amount of dopamine suggesting that the SNC80-released glutamate is insufficient in the perfusion system to release dopamine. However, this does not explain why SNC80 fails to release dopamine as measured by *in vivo* microdialysis (Longoni et al., 1998).

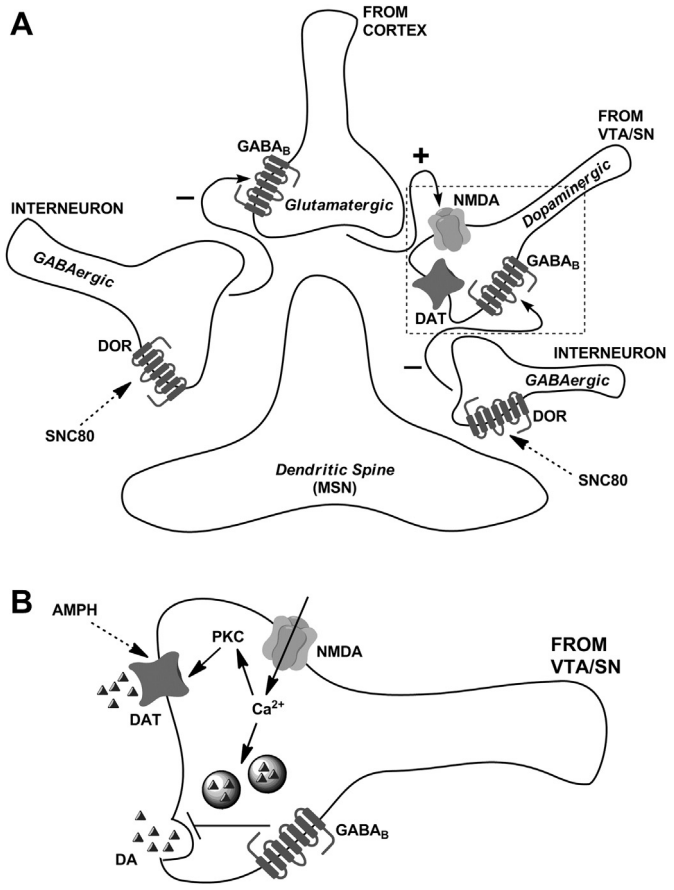

Fig. 8. Proposed mechanism of interaction between DOR agonists and amphetamine on dopamine efflux and related behaviors. A) Striatal glutamate release from cortical glutaminergic efferent neurons and dopamine release from projection neurons from the ventral tegmentum area (VTA) or substantia nigra (SN) is negatively regulated by GABA released from striatal GABAergic interneurons. Inhibition of GABA release by DOR agonists (e.g. SNC80) may enhance glutamate release and dopamine release. The released glutamate activates NMDA receptors on terminals of dopaminergic projection neurons. B) NMDA activation leads to an influx of Ca^{2+} that causes exocytotic release of dopamine and/or other intracellular processes (such as activation of PKC) that may enhance amphetamine-mediated release of dopamine efflux through the dopamine transporter (DAT).

The mechanism by which glutamate signaling through NMDA receptors synergistically stimulates dopamine release in combination with amphetamine is unknown. The ability of both glutamic acid and SNC80 (Bosse et al., 2008) to augment amphetamine-mediated dopamine efflux was seen to be dependent on extracellular Ca^{2+}. Glutamate activation of ionotropic receptors, such as NMDA receptors, leads to Ca^{2+}-dependent exocytotic release of dopamine whereas amphetamine promotes dopamine efflux through direct interaction with the dopamine transporter (Fig. 8). Activation of these two processes would presumably result in additive effects on dopamine efflux as demonstrated previously (Bowyer et al., 1991). Alternatively, the influx of Ca^{2+}, following glutamatergic stimulation of NMDA receptors, could mediate other cellular events, in particular translocation of protein kinase C (PKC) from the cytosol to the membrane and PKC activation (Ho et al., 1988; TerBush et al., 1988), which has been shown to increase amphetamine-stimulated outward transport of dopamine from perfused rat striatal slices (Kantor and Gnegy, 1998). Future studies will evaluate the possible roles of exocytotic dopamine release, PKC, and DA transporter phosphorylation in the synergistic interactions between SNC80 and amphetamine. Additionally, the contribution of other glutamatergic and GABAergic receptor subtypes in these neurochemical and behavioral effects will be evaluated.

5. Conclusions

The present findings indicate the DOR agonist, SNC80, potentiates amphetamine-stimulated dopamine efflux in the striatum through an indirect mechanism involving disinhibition of glutamate efflux followed by stimulation of NMDA receptors and inhibition of GABA efflux. This mechanism presumably underlies, or at least contributes to, the enhancement of amphetamine-stimulated locomotor activity observed with SNC80 (Jutkiewicz et al., 2008). Interactions between dopamine, glutamate and GABA neurotransmission have been implicated in the initiation of drug-taking and transition to compulsive drug-seeking in addiction (Kalivas and Volkow, 2005) as well as multiple neuropathological conditions, such as Parkinson's disease, schizophrenia, and epilepsy (Carlsson and Carlsson, 1990; Chapman, 1998). Hence, the study of the neuromodulatory role of DOR agonists on these systems may provide new insights to understanding these diseases and targets for drug therapies.

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