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Effects of memantine alone and with acute 'binge' cocaine on hypothalamic–pituitary–adrenal activity in the rat

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Abstract

The effects of memantine, a non-competitive NMDA-receptor antagonist used in the management of dementia, and its coadministration with acute 'binge' pattern cocaine on hypothalamic–pituitary–adrenal axis activity were investigated in the rat. Measurements 3 h after injections showed that memantine alone at 20 mg kg^{-1} (i.p.), but not 10 mg kg^{-1}, increased corticotropin-releasing factor (CRF) mRNA levels in the hypothalamus and both adrenocorticotropic hormone and corticosterone levels in the blood, and decreased type I CRF receptor mRNA in the anterior pituitary. Our previous studies have shown that acute 'binge' cocaine increases CRF mRNA levels in the hypothalamus. In this study, pretreatment with memantine (10 and 20 mg kg^{-1}, i.p.) did not alter the up-regulation of hypothalamic CRF mRNA induced by acute 'binge' cocaine (3×15 mg kg^{-1}, i.p.). Of interest, pretreatment with memantine at 10 mg kg^{-1}, which alone had no effect on corticosterone levels, caused a greater elevation of corticosterone levels in combination with 'binge' cocaine than acute 'binge' cocaine alone, indicating that memantine does not attenuate 'binge' cocaine-stimulated hypothalamic–pituitary–adrenal activity. These results indicate that both memantine and acute 'binge' cocaine stimulate hypothalamic–pituitary–adrenal activity by activating CRF neurons in the hypothalamus.

Keywords: Memantine; 'Binge' cocaine; CRF (corticotropin-releasing factor); CRF_1 receptor; HPA axis; Solution hybridization; RNase protection

1. Introduction

Memantine (1-amino-3,5-dimethyl-adamantane), a low affinity noncompetitive NMDA-receptor ligand, binds to NMDA receptors and antagonizes NMDA-induced responses (Bormann, 1989; Kornhuber et al., 1989; Chen et al., 1992; Wenk et al., 1994). Memantine, a dimethyl derivative of amantadine, has been used extensively, primarily in Europe, in the management of Parkinson's disease, Alzheimer's disease and other forms of dementia (Greenamyre et al., 1988; Ditzler, 1991). Recently in an experimental study, systemic administration of memantine has been demonstrated to produce a dose-dependent increase in extracellular dopamine content in the rat striatum, suggesting an interaction between memantine and dopamine systems (Spanagel et al., 1994). In contrast, systemic administration of a high affinity non-competitive NMDA receptor antagonist MK-801 ((+)-5-methyl-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5,10-imine maleate) has been reported to have an inhibitory effect at 0.25 to 2 mg kg^{-1} dosage (Kashihara et al., 1990) or no effect at 0.5 mg kg^{-1} (Weihmuller et al., 1991) on extracellular dopamine levels in the striatum, showing the mechanistic differences between these two compounds. An important stimulatory role for dopamine systems in regulation of hypothalamic–pituitary–adrenal axis has been demonstrated (Borowsky and Kuhn, 1992). Therefore, memantine by altering dopamine activity might also contribute to regulation of the hypothalamic–pituitary–adrenal axis. Of interest, acute administration of MK-801 at a wide dose range (0.12 to 1.2 mg kg^{-1}) has been reported to increase adrenocorticotropic hormone (ACTH) and corticosterone secretion (Pechnick et al., 1989), despite that the fact that it has no effect on extracellular dopamine content in the forebrain when administered systemically. Acute administration of MK-801 at a high dose (1 mg kg^{-1}) also

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has been shown to stimulate corticotropin-releasing factor (CRF) mRNA expression in the paraventricular nucleus of the hypothalamus (Lee et al., 1994).

Most of cocaine's effects (such as reinforcing properties, psychomotor stimulant and euphoric effects) are related to the inhibition of dopamine re-uptake at nerve terminals. In the rat, acute cocaine administration increases plasma ACTH, β-endorphin and corticosterone levels (Moldow and Fischman, 1987). Pretreatment with both D_1 and D_2 type dopamine receptor antagonists attenuates the stimulatory effects of cocaine on hypothalamic–pituitary–adrenal activity, providing evidence that the stimulation is mediated by increased synaptic dopamine (Borowsky and Kuhn, 1991; Spangler et al., 1997). The fact that peripheral administration of CRF-antiserum entirely blunts acute cocaine-induced ACTH secretion in the rat has demonstrated a CRF-mediated mechanism (Rivier and Vale, 1987). Furthermore, acute cocaine administration increases CRF mRNA levels in the paraventricular nucleus measured by in situ hybridization (Rivier and Lee, 1994). We also have recently found by quantitative solution hybridization assays, that acute 'binge' pattern cocaine administration elevates hypothalamic CRF mRNA expression, without alterations of type I CRF receptor (CRF_1 receptor) or pro-opiomelanocortin (POMC) mRNA in the anterior pituitary (Zhou et al., 1996b). Of interest, chronic (12 days) coadministration of MK-801 with cocaine every other day has been reported to block the corticosterone release induced by cocaine challenge following 21 days withdrawal (Damianopoulos and Carey, 1995).

It is not known whether memantine alone exerts any effects on the hypothalamic–pituitary–adrenal axis. It is also not known whether or not memantine pretreatment attenuates cocaine-stimulated hypothalamic-pituitary–adrenal activity. Therefore, in the present study, we examined (1) the effect of memantine alone on hypothalamic–pituitary–adrenal activity (including CRF mRNA levels in the hypothalamus, CRF_1 receptor and POMC mRNA levels in the pituitary and plasma ACTH and corticosterone levels); and (2) the effect of memantine pretreatment on acute 'binge' cocaine-stimulated hypothalamic–pituitary–adrenal activity.

2. Materials and methods

Male Fischer rats (190–220 g, Charles River Labs., Kingston, NY) were housed individually in a stress-minimized facility with free access to food and water. Animals were adapted to a standard 12-h light/dark cycle (lights on from 9:00 h to 21:00 h) for seven days. Before drug administration, all animals were handled and received three daily intraperitoneal (i.p.) injections of saline (3 ml kg^{-1} day^{-1}) at 9:30 h, 10:30 h and 11:30 h for 6 days in order to minimize injection-induced stress by the time the experiment began (a method validated in earlier studies, see Zhou et al., 1996b). On day 7, animals received one day of i.p. injections of cocaine (3×15 mg kg^{-1}) or equal volume of saline (3×1 ml kg^{-1}) in their home cages following the 'binge' pattern regimen: three times daily at 1 h intervals (9:30, 10:30, and 11:30) (Branch et al., 1992). All animals were pretreated with a single injection of either saline (1 ml kg^{-1} i.p.) or memantine (10 or 20 mg kg^{-1}, i.p.) 30 min before the first injection of the 'binge' cocaine or saline administration.

The experiment had six groups of animals: (1) saline + saline: saline followed by 'binge' saline; (2) saline + cocaine: saline followed by 'binge' cocaine; (3) memantine 10 + saline: memantine (10 mg kg^{-1}) followed by 'binge' saline; (4) memantine 10 + cocaine: memantine (10 mg kg^{-1}) followed by 'binge' cocaine; (5) memantine 20 + saline: memantine (20 mg kg^{-1}) followed by 'binge' saline; and (6) memantine 20 + cocaine: memantine (20 mg kg^{-1}) followed by 'binge' cocaine.

Animals were exposed to CO_2 for 15 s and sacrificed by decapitation at 12:00 h, 30 min after the final saline or cocaine injection. The hypothalamus, anterior lobe and neurointermediate lobe/posterior lobe of the pituitary were dissected on ice, homogenized in guanidinium thiocyanate buffer and extracted with acidic phenol and chloroform.

A 760-base pair fragment from the rat CRF cDNA (a kind gift from Dr. R.C. Thompson at The University of Michigan) or a 538 base pair fragment from the rat POMC cDNA (a kind gift from Dr. J.L. Roberts at The Mount Sinai Medical Center in New York) was cloned into the polylinker region of the pSP64 plasmid (Promega, Madison, WI) in both the sense and antisense orientations. A portion of the human 18S rRNA gene inserted into the plasmid pS/E (a pSP65 derivative) was a kind gift from Drs. T. Nilsen and P. Maroney at Case Western University. ^{33}P-labeled cRNA antisense probes and unlabeled RNA sense standards were synthesized using a SP6 transcription system. ^{33}P-labeled CRF_1 receptor antisense probe was synthesized using the SP6 polymerase from the pcDNA plasmid, which contains a 2.5-kb fragment from the rat CRF_1 receptor cDNA (a kind gift from Dr. W. Vale at The Salk Institute), and its RNA sense standard was synthesized from the opposite orientation using the T7 polymerase from the same pcDNA plasmid. A denaturing agarose gel was used to insure that a single full-length transcript had been synthesized from each plasmid.

The solution hybridization RNase protection–trichloroacetic acid precipitation protocol for POMC, CRF or CRF_1 receptor has recently been described in detail and documentation of the protected fragment by gel electrophoresis included in these reports (Zhou et al., 1996a, b). A set of sense RNA calibration standards with known amounts of an in vitro synthesized sense transcript (the concentration was determined by optical absorbance at 260 nm) was used to relate values obtained from experimental samples (brain or pituitary RNA) to specific RNA levels. The optimal hybridization conditions were 50% formamide and

75°C for POMC, 10% formamide and 75°C for CRF_1 receptor, and no formamide and 75°C for CRF. A new standard curve was generated each time experimental samples were analyzed and all RNA extracts of a particular tissue were assayed for each mRNA as a group on a single day. Total cellular RNA concentrations were measured by hybridization of diluted extracts to a ^{33}P-labeled probe complementary to 18S rRNA at 75°C.

At the time of decapitation of each rat, trunk blood was collected in tubes placed on ice, spun in a refrigerated centrifuge, and plasma was separated and stored at −20°C. Corticosterone levels were assayed using a rat corticosterone ^{125}I kit (ICN Biomedicals, Costa Mesa, CA). Briefly, plasma samples were diluted 25–200 fold, mixed with ^{125}I-labeled corticosterone, and incubated with a specific antiserum. Cross-reactivity of the antibody with deoxycorticosterone, testosterone, aldosterone, progesterone, estriol or estrone is reported to be < 0.5% (ICN Biomedicals, CA). After incubation, the corticosterone bound to antibody was precipitated by a mixture of polyethylene glycol and goat antirabbit gamma globulins. Intra-assay coefficients of variation were 1.5%. ACTH levels were assayed from unextracted plasma using a two-site IRMA assay (Allegro Nichols Immunoassay Nichols Institute, San Juan Capistrano, CA). Briefly, plasma samples were incubated with a ^{125}I-labeled monoclonal antibody and a polyclonal antibody. The antibody–ACTH complex was then precipitated via the high affinity interaction between avidin and biotin conjugated reactants. Intra-assay coefficients of variation were 4.1%. All ACTH or corticosterone values were determined in duplicate in a single assay.

Data are presented graphically as the mean ± S.E.M. To evaluate the statistical significance of differences between treatment groups, two-way analyses of variance (ANOVA) (Factor 1: saline, memantine 10, memantine 20; Factor 2: saline, cocaine) followed by Neuman–Keuls post-hoc tests were used. To assure that our previous finding of corticosterone elevation induced by 'binge' cocaine was replicated in this study with saline pretreatment, a preliminary *t*-test (saline + saline vs. saline + cocaine treatment group) was conducted. The accepted level of significance for all tests was $P < 0.05$.

3. Results

3.1. Effects of memantine alone or memantine pretreatment prior to acute 'binge' cocaine on CRF mRNA levels in the hypothalamus

Administration of memantine at 20 mg kg^{-1} (i.p.) significantly increased CRF mRNA levels in the hypothalamus (two-way ANOVA followed by Neuman–Keuls post-hoc tests, memantine 20 + saline vs. saline + saline, $P < 0.05$) (Fig. 1). There was no significant change when the rats were given 10 mg kg^{-1} of memantine.

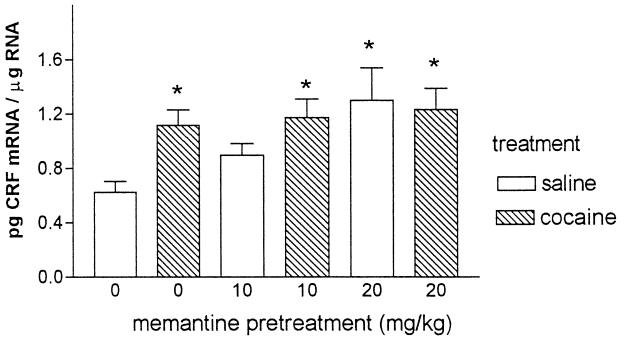

Fig. 1. Effects of saline or memantine pretreatment prior to administration of acute 'binge' pattern cocaine (3×15 mg kg^{-1}, i.p.) or 'binge' pattern saline on CRF mRNA levels (expressed as mean ± S.E.M. pg CRF mRNA per μg total RNA of the extract) in the hypothalamus. Saline pretreatment, $n = 11$; memantine pretreatment, $n = 6$. * $P < 0.05$ vs. saline pretreatment/no cocaine.

Acute 'binge' cocaine administration (15 mg kg^{-1}, 1 h × 3) caused a significant increase in hypothalamic CRF mRNA levels (saline + cocaine vs. saline + saline, $P < 0.05$) (Fig. 1), as we reported previously (Zhou et al., 1996b). 'Binge' cocaine groups pretreated with either 10 or 20 mg kg^{-1} of memantine also showed a significant increase in CRF mRNA levels, compared to saline control (memantine 10 + cocaine vs. saline + saline, $P < 0.05$;

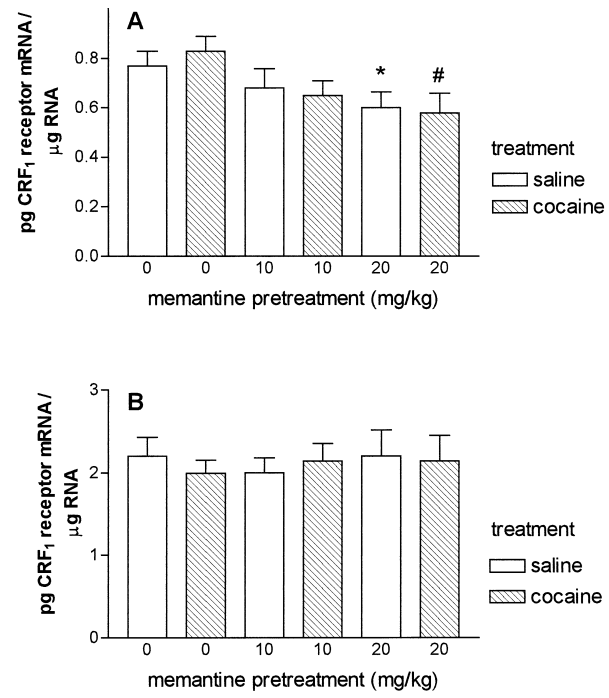

Fig. 2. Effects of saline or memantine pretreatment prior to administration of acute 'binge' pattern cocaine (3×15 mg kg^{-1}, i.p.) or 'binge' pattern saline on CRF_1 receptor mRNA levels (expressed as mean ± S.E.M. pg CRF_1 receptor mRNA per μg total RNA of the extract) in the anterior lobe of the pituitary (A) and the neurointermediate lobe/posterior lobe of the pituitary (B). Saline pretreatment, $n = 10–12$; memantine pretreatment, $n = 5–6$. * $P < 0.01$ vs. saline pretreatment/no cocaine; #: $P < 0.01$ vs. saline pretreatment/'binge' cocaine.

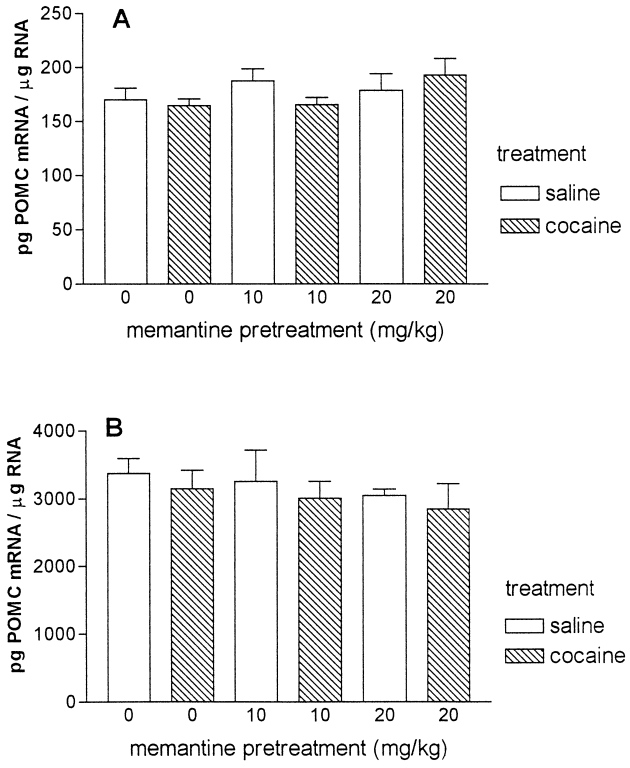

Fig. 3. Effects of saline or memantine pretreatment prior to administration of acute 'binge' pattern cocaine (3×15 mg kg^{-1}, i.p.) or 'binge' pattern saline on POMC mRNA levels (expressed as mean ± S.E.M. pg POMC mRNA per μg total RNA of the extract) in the anterior lobe of the pituitary (A) and the neurointermediate lobe/posterior lobe of the pituitary (B). Saline pretreatment, $n = 11$–12; memantine pretreatment, $n = 6$. No significant differences were found.

memantine 20 + cocaine vs. saline + saline, $P < 0.05$) (Fig. 1). These elevations were of similar magnitude to that found in the rat treated with acute 'binge' cocaine alone.

3.2. Effects of memantine alone or memantine pretreatment prior to acute 'binge' cocaine on CRF_1 receptor mRNA levels in the anterior lobe and neurointermediate lobe / posterior lobe of the pituitary

Administration of memantine at 20 mg kg^{-1} (i.p.) significantly decreased CRF_1 receptor mRNA levels in the anterior pituitary (two-way ANOVA followed by Neuman–Keuls post-hoc tests, memantine 20 + saline vs. saline + saline, $P < 0.01$) (Fig. 2A). There was no significant change when the rats were given 10 mg kg^{-1} of memantine.

Acute 'binge' cocaine administration (15 mg kg^{-1}, 1 h $\times$ 3) did not produce any changes in the levels of CRF_1 receptor mRNA in the anterior pituitary, a result identical to our previous findings (Zhou et al., 1996b) (Fig. 2A). When memantine and 'binge' cocaine were given together, the CRF_1 receptor mRNA reduction was similar to that found in the rat treated with memantine alone.

There were no effects on CRF_1 receptor mRNA levels in the neurointermediate lobe/posterior lobe of the pituitary by memantine alone, acute 'binge' cocaine alone or memantine in combination with 'binge' cocaine (Fig. 2B).

3.3. Effects of memantine alone or memantine pretreatment prior to acute 'binge' cocaine on POMC mRNA levels in the anterior lobe and neurointermediate lobe / posterior lobe of the pituitary

There were no effects on POMC mRNA levels either in the anterior lobe (Fig. 3A) or in the neurointermediate lobe/posterior lobe (Fig. 3B) of the pituitary by memantine alone, acute 'binge' cocaine alone or memantine in combination with 'binge' cocaine.

3.4. Effects of memantine alone or memantine pretreatment prior to acute 'binge' cocaine on plasma ACTH and corticosterone levels

Administration of memantine at 20 mg kg^{-1} (i.p.) significantly elevated ACTH levels in the blood (two-way

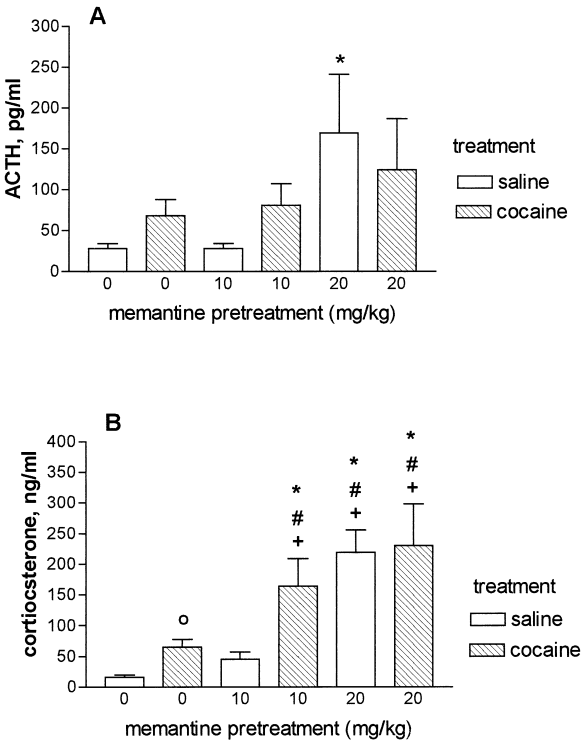

Fig. 4. Effects of saline or memantine pretreatment prior to administration of acute 'binge' pattern cocaine (3×15 mg kg^{-1}, i.p.) or 'binge' pattern saline on plasma ACTH (A) (expressed as mean pg ml^{-1} ± S.E.M.) and corticosterone levels (B) (expressed as mean ng/ml ± S.E.M.). Saline pretreatment, $n = 15$–17; memantine 10 pretreatment, $n = 11$–12; memantine 20 pretreatment, $n = 6$. (A) $*$ $P < 0.05$ vs. saline pretreatment/no cocaine. (B) ○: $P < 0.05$ (t-test) vs. saline pretreatment/no cocaine; $*$ $P < 0.01$ vs. saline pretreatment/no cocaine; #: $P < 0.01$ vs. saline pretreatment/'binge' cocaine; +: $P < 0.01$ vs. memantine (10 mg kg^{-1}) pretreatment/no cocaine.

ANOVA followed by Neuman–Keuls post-hoc tests, memantine 20 + saline vs. saline + saline, $P < 0.05$) (Fig. 4A).

Administration of memantine at 20 mg kg^{-1} (i.p.) significantly elevated corticosterone levels in the blood (two-way ANOVA followed by Neuman–Keuls post-hoc tests, memantine 20 + saline vs. saline + saline, $P < 0.0005$) (Fig. 4B). There was no significant change when the rats were given 10 mg kg^{-1} of memantine.

Acute 'binge' cocaine administration (15 mg kg^{-1}, 1 h × 3) caused a significant elevation of plasma corticosterone levels ($t_{(1,30)} = 13.23$, saline + cocaine vs. saline + saline, $P < 0.005$) (Fig. 4B), as reported previously (Zhou et al., 1996b). 'Binge' cocaine with 10 mg kg^{-1} of memantine pretreatment caused a greater elevation of corticosterone levels than treatment with either acute 'binge' cocaine alone (memantine 10 + cocaine vs. saline + cocaine, $P < 0.01$) or 10 mg kg^{-1} of memantine alone (memantine 10 + cocaine vs. memantine 10 + saline, $P < 0.005$). Although 'binge' cocaine with 20 mg kg^{-1} of memantine pretreatment also had greater effects than acute 'binge' cocaine alone (memantine 20 + cocaine vs. saline + cocaine, $P < 0.005$), there was no greater effect than treatment with 20 mg kg^{-1} of memantine alone.

4. Discussion

Memantine treatment at 20 mg kg^{-1} produced a significant increase in CRF mRNA levels in the hypothalamus, suggesting enhanced CRF biosynthesis. The elevation of hypothalamic–pituitary–adrenal activity, as reflected by both ACTH and corticosterone elevations in the blood three hours after the memantine administration, may be related to enhanced CRF activity. A glutamatergic innervation has been demonstrated in the hypothalamus arising from the glutamate-synthesizing cells of the hippocampus, and glutamate receptors are widely distributed in the hypothalamic region (van de Pol et al., 1990). Although the mechanisms are not yet known, one cannot rule out the possibility that stimulation of CRF neurons may be indirectly mediated through hypothalamic dopaminergic systems, GABAergic systems or opioid systems. Our data showing a stimulatory effect of memantine on the hypothalamic–pituitary–adrenal axis suggest a mechanism mediated by hypothalamic CRF.

Spanagel and colleagues have examined the concentration profile of memantine in two rat brain regions after a single i.p. injection of 10 and 20 mg kg^{-1}; that study showed that the maximal concentrations of memantine are reached in the brain 60–80 min after the injection and the elimination half-life is 126–205 min (Spanagel et al., 1994). The above information on the pharmacokinetics of memantine shows that memantine is a relatively long-acting compound in the rat. Our results showing the stimulation of the HPA activity 3 h after a single injection of memantine at 20 mg kg^{-1} also suggests a relatively long-acting effect of memantine, which may be related to its long-lasting pharmacokinetic profile. Compared with memantine, MK-801 has been reported to have relatively shorter-lasting effects and the effect on plasma β-endorphin secretion was over by 120 min after a single injection (Contreras et al., 1991).

It has been shown that MK-801 at 0.12–1.2 mg kg^{-1} doses stimulates ACTH and corticosterone secretion 60 min after administration (Pechnick et al., 1989), and MK-801 at 1 mg kg^{-1} increases CRF mRNA expression in the paraventricular nucleus 60 min after administration (Lee et al., 1994). Although several groups did not observe any effects, or even a decrease, on striatal extracellular dopamine levels by systemic administration of MK-801 (Kashihara et al., 1990; Weihmuller et al., 1991), Imperato et al. (1990) reported an increase in extracellular dopamine levels by direct infusion of MK-801 into the nucleus accumbens and caudate-putamen of the rat. It is not known whether the stimulatory effects of MK-801 on the hypothalamic–pituitary–adrenal axis are related to striatal dopamine levels. Indeed, systemic administration of memantine increased extracellular dopamine levels in the rat striatum (Spanagel et al., 1994), and stimulated hypothalamic–pituitary–adrenal activity in the present study.

As we reported previously, acute 'binge' cocaine administration elevated both CRF mRNA levels in the hypothalamus and corticosterone levels in the blood (Zhou et al., 1996b). In this present study, we found that in spite of corticosterone levels elevated at the time point 2.5 h after the first 'binge' cocaine injection, no significant ACTH elevation was found. Torres and Rivier have reported that cocaine injection (5 mg kg^{-1} injection^{-1}) at a 1 h dosing interval causes a significant attenuation of ACTH response following the third injection of the same amount of cocaine in the rat, due to acute negative feedback mechanism of glucocorticoids on ACTH release from the anterior pituitary (Torres and Rivier, 1992). This attenuation effect might explain lower corticosterone elevation without significant ACTH elevation induced by 'binge' cocaine administration in our experiment, in which a higher dose of cocaine (15 mg kg^{-1} injection^{-1}) was administered.

The experiment of coadministration of memantine and acute 'binge' cocaine was designed to examine whether memantine pretreatment alters hypothalamic–pituitary–adrenal responses to acute 'binge' cocaine. If 'binge' cocaine-stimulated hypothalamic–pituitary–adrenal activity is mediated through NMDA receptors, a reduction should be observed after memantine pretreatment prior to 'binge' cocaine. However, pretreatment with memantine at 10 mg kg^{-1}, which alone had no significant effect on ACTH or corticosterone levels, produced a greater corticosterone elevation than 'binge' cocaine alone, an apparent additive response, but no change in levels of ACTH. In addition, memantine pretreatment prior to 'binge' cocaine

did not alter the magnitude of CRF mRNA elevation induced by 'binge' cocaine alone.

Concurrent with increases in corticosterone levels, as well as ACTH levels, in the blood, memantine at 20 $mg\,kg^{-1}$ decreased CRF_1 receptor mRNA levels in the anterior pituitary. It has been demonstrated that CRF_1 receptor mRNA expression is subject to negative feedback control by glucocorticoids (Pozzoli et al., 1996; Zhou et al., 1996a). The high dose of memantine (20 mg kg^{-1}) caused greater (about 3–4 fold) stimulatory effects on corticosterone secretion than either the low dose of memantine (10 mg kg^{-1}) or 'binge' cocaine, suggesting that significant increases of endogenous glucocorticoids may contribute to the inhibition of CRF_1 receptor mRNA expression in the anterior pituitary.

It has also been reported that elevated levels of portal CRF may contribute to either down-regulation of CRF receptor binding (Hauger and Aguilera, 1993) or decreases in CRF_1 receptor mRNA levels in the anterior pituitary in adrenalectomized rats (Sakai et al., 1996). However, administration of exogenous CRF (100 $\mu g\ kg^{-1}\ day^{-1}$) twice daily for 5 days was found to have no effect on CRF_1 receptor mRNA levels in the anterior pituitary in intact rats (Zhou et al., 1996a). Also, in the present study, we found no reduction of CRF_1 receptor mRNA levels in rats treated with 'binge' cocaine, which caused similar CRF mRNA level elevations as were observed in the rat treated with 20 $mg\,kg^{-1}$ of memantine.

Another hypothalamic secretagogue arginine vasopressin has been reported to potentiate CRF-induced down-regulation of CRF_1 receptor binding (Hauger and Aguilera, 1993). Also, arginine vasopressin potentiates CRF-stimulated POMC peptide secretion in rats (Holmes et al., 1986; Plotsky, 1987). However, arginine vasopressin does not play a significant role in acute cocaine-induced ACTH release (Rivier and Lee, 1994). Therefore, it is possible that arginine vasopressin is simultaneously stimulated by memantine, which could contribute to the observed decreases in CRF_1 receptor mRNA levels.

In summary, our findings indicate that both memantine and acute 'binge' cocaine exert their stimulatory effects on the hypothalamic–pituitary–adrenal axis by activating CRF neurons in the hypothalamus. These results also show that memantine pretreatment does not attenuate acute 'binge' cocaine-induced increases in CRF mRNA levels and hypothalamic–pituitary–adrenal activity.

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