12. EFFECT OF MDMA-LIKE DRUGS ON CNS NEUROPEPTIDE SYSTEMS

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1. INTRODUCTION

The ring-substituted amphetamine analogue, 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") causes in humans psychoactive responses described as a combination of euphoria, enhanced empathy, and central stimulation [1]. This combination of pharmacological effects has caused MDMA to become a popular recreational drug, resulting in its classification as a Schedule I agent. Comparisons with other psychoactive drugs have demonstrated that MDMA and another amphetamine analogue, 3,4-methylenedioxyamphetamine (MDA), possess both stimulant properties, resembling more traditional amphetamine congeners, and hallucinogenic activity, like LSD [2]. This somewhat unique combination of effects has caused some investigators to claim that these so-called "designer" amphetamine analogues represent a new class of pharmacological agents [3, 4].

All findings to date suggest that the MDMA-like drugs exert their pharmacological activity by altering monoaminergic systems. In particular, stimulation of serotonergic and dopaminergic pathways are throught to mediate the psychoactive effects of these compounds. While the relative involvement of serotonin (5-HT) and dopamine (DA) in mediating the pharmacological properties of such drugs is still an issue of controversy, most investigators consider serotonergic pathways as the primary effector transmitter system for these agents. In support of this hypothesis are the findings (1) that these designer amphetamine analogues are more potent at releasing 5-HT than at

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releasing dopamine [5, 6] and (2) that high doses of both MDMA and MDA selectively damage serotonergic neurons, causing long-term and dramatic decreases in brain levels of 5-HT and the activity of its synthesizing enzyme, tryptophan hydroxylase, while having little detectable impact on dopamine concentration or the activity of its synthesizing enzyme, tyrosine hydroxylase [7, 8, 9].

In spite of the somewhat selective effects on serotonergic pathways by MDMA and MDA, there is evidence that these drugs also significantly increase central nervous system dopaminergic activity. In vitro studies reveal that MDMA is a potent releaser of dopamine through action on the carrier mechanism [5]. In vivo voltametric detection of extracellular dopamine has been used to demonstrate that MDMA administered systemically results in substantial dopamine release from striatum and nucleus accumbens [10]. These findings have been supported by behavioral studies that suggest that MDMA and MDA have amphetamine-like stimulant properties thought to be dopaminergically-mediated [2]. However, in contrast to the serotonergic responses, traditional neurochemical markers used to monitor changes in the activity of the dopaminergic system are little affected by administration of the designer amphetamines. For example, the only dopaminergic changes of significance in the rat include a transient elevation in striatal levels of dopamine and its metabolite, homovanillic acid, following a single dose of MDMA and MDA [9]. Such a change likely reflects a drug-mediated increase in dopamine release. In addition, Stone and coworkers [11] reported that two weeks following multiple doses of MDMA, the striatal contents of dopamine metabolites were slightly lower than corresponding controls, but in animals treated with MDA or another designer amphetamine, N-ethyl-3,4-methylenedioxyamphetamine (MDE), these metabolites remained unaltered. In neither study were changes in tyrosine hydroxylase activity seen following drug treatments.

Interestingly, single and possibly multiple doses of amphetamine or its methylated analogue, methamphetamine, also result in initial transient rises in the levels of dopamine metabolites. These rises are comparable to those observed following MDMA and MDA administration [12, 13]; however, unlike the designer amphetamines, profound long-term decreases (thought to be related to neurotoxic drug effects) occur in tyrosine hydroxylase activity and in the concentrations of dopamine and its metabolites, following multiple doses of both amphetamine or methamphetamine [14, 15].

Based on the above cited changes in dopaminergic neurochemical parameters, there are uncertainties as to how the designer amphetamines compare to amphetamine and methamphetamine in their ability to activate dopaminergic pathways. Apparently, neurochemical evaluation of the dopaminergic systems themselves is not sufficient to answer many of the questions concerning the impact of the designer amphetamines on these pathways. Another approach worth investigating is proposed here and consists of determining the response of transmitter systems that are "downstream" from the dopami-

nergic pathways. In other words, these downstream systems, due to their neuronal linkage to dopamine projections, are altered by drug-induced fluctuations in postsynaptic dopaminergic activity. Consequently, if such downstream pathways could be identified and their response to changes in dopaminergic activity could be characterized, neurochemical analysis of these pathways following treatments with drugs such as the designer amphetamines would be useful tools for establishing the dopaminergic consequences of these agents.

Within extrapyramidal structures there exist neuropeptide pathways that are dramatically influenced by changes in the postsynaptic activity of the nigral-striatal dopaminergic neurons. However, these same extrapyramidal peptide systems do not appear to respond directly to fluctuations in serotonergic activity [16, 17, unpublished observations]. The transmitter substances of these responsive peptidergic projections include substance P (SP), neurotensin (NT), and dynorphin A_{1-17} (Dyn). Specifically, SP-containing neurons, which originate within the striatum and terminate in the substantia nigra, are thought to serve an excitatory feedback function to the nigral-striatal dopamine pathway. In support of this hypothesis is the observation that intranigral injections of SP cause striatal release of dopamine [18] and stimulate locomotion [19]. As would be expected, nigral administration of SP has no locomotor effects in animals that have received 6-hydroxydopamine lesions to their mesostriatal dopamine pathway [19]. The state of this SP pathway is reciprocally controlled by dopaminergic activity causing striatal and nigral content of SP to increase or decrease in response to repeated increases or decreases, respectively, in nigral-striatal dopaminergic activity [16, 20].

The interactions between neurotensin pathways and the extrapyramidal dopaminergic system are somewhat more complex. As the vast majority of striatal and nigral neurotensin receptors are associated with dopamine neurons [21], neurotensin pathways certainly contribute to the regulation of extrapyramidal dopamine activity. The overall CNS pharmacology of neurotensin has been compared to that of the neuroleptic drugs [22], whereas intraventricular administration of this peptide is reported to antagonize some of the behavioral activity of powerful stimulants, such as amphetamine and cocaine [23]. Short-term or long-term increases in mesostriatal dopaminergic activity cause dramatic but transient elevations in striatal and nigral levels of neurotensin [24]. Finally, dynorphin A is associated with striatal-nigral neurons, which, like the SP pathway, have been postulated to be part of a feedback system to the nigral-striatal dopamine neurons [25]. Increases in activity of the mesostriatal dopamine pathway cause a relatively rapid rise in both striatal and nigral dynorphin concentrations [26]. However, such a feedback role for dynorphin has recently been questioned, as the locomotor activity induced by nigral dynorphin injections is not influenced by elimination of the nigral-striatal dopamine pathway [19].

The effects of the designer amphetamine analogues on SP, neurotensin, and dynorphin pathways associated with extrapyramidal structures have been

evaluated. For comparison, the responses of these peptide systems in the nucleus accumbens, a limbic structure, were also determined in some of the experiments. Following the systemic administration of drugs such as MDMA and MDA, changes in the neuropeptide systems were assessed by radioimmunoassay, measuring striatal and nigral content of SP [20], neurotensin [24], and dynorphin [26] immunoreactivity. The antibodies employed in the assays were raised in our laboratory and are highly selective and able to detect 2-8 pg of neuropeptide per sample. The mean neuropeptide contents (pg/mg protein) detected were as follows: striatum — SP = 1,740, neurotensin = 148, dynorphin = 380; substantia nigra — SP = 12,400, neurotension = 501, dynorphin = 760; nucleus accumbens — neurotensin = 377, dynorphin = 823. Differences between treatment groups were assessed employing either the Student's *t*-test or an ANOVA analysis followed by a multiple comparisons test. Significance was judged to occur at the 0.05 level.

2. EFFECT OF MDMA AND RELATED AGENTS ON NEUROPEPTIDES

The responses of SP, neurotensin, and dynorphin extrapyramidal systems to the designer amphetamines were determined and compared to the changes induced by methamphetamine treatment. Sprague–Dawley rats received five doses (six-hour intervals between doses) of MDMA (10 mg/kg/dose), MDA (10 mg/kg/dose), and methamphetamine (15 mg/kg/dose). Approximately 18 hours following treatment, the animals were decapitated and brains were removed. The striata and substantia nigras were dissected out, and for some experiments, the nucleus accumbens was also excised. The tissues were prepared for radioimmunoassay analysis as previously described [20, 24, 26], and the peptide levels were normalized by the total protein content in each sample.

The striatal content of SP was increased to approximately 200% of control by the administration of all three drugs examined. In the substantia nigra, both MDA and methamphetamine administration increased SP content to 150%, whereas MDMA treatment elevated SP levels only to an insignificant 127% of control (Figure 1).

The responses of the neurotensin systems were examined by giving multiple administrations (as described for Figure 1) of two doses of both MDMA (10 or 15 mg/kg/dose) and MDA (5 or 10 mg/kg/dose), as well as one dose of methamphetamine (15 mg/kg/dose). In the striatum and nucleus accumbens, 200–300% increases in neurotensin levels were observed following all drug treatments (Figure 2). However, increases in nigral NT content following both doses of MDMA were about half that found in animals treated with either dose of MDA or methamphetamine.

The responses by the dynorphin projections were studied in animals that were treated with either five administrations of MDMA (10 mg/kg-dose) or of methamphetamine (15 mg/kg/dose). Treatment with either drug increased nigral dynorphin levels to approximately 250% of control (Figure 3). However, MDMA treatment appeared to have substantially less effect on dynorphin

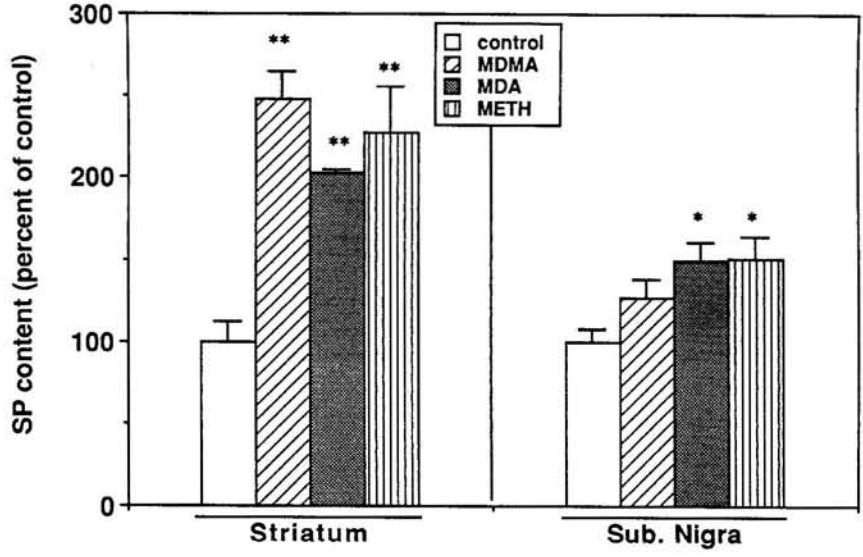

Figure 1. Effects of MDMA, MDA, and methamphetamine on the levels of substance P in extrapyramial structures. Rats were sacrificed 18 hours following 5 doses (6-hour intervals between doses) of MDMA, MDA, or METH. *$P < 0.01$ and **$P < 0.005$ compared to corresponding controls.

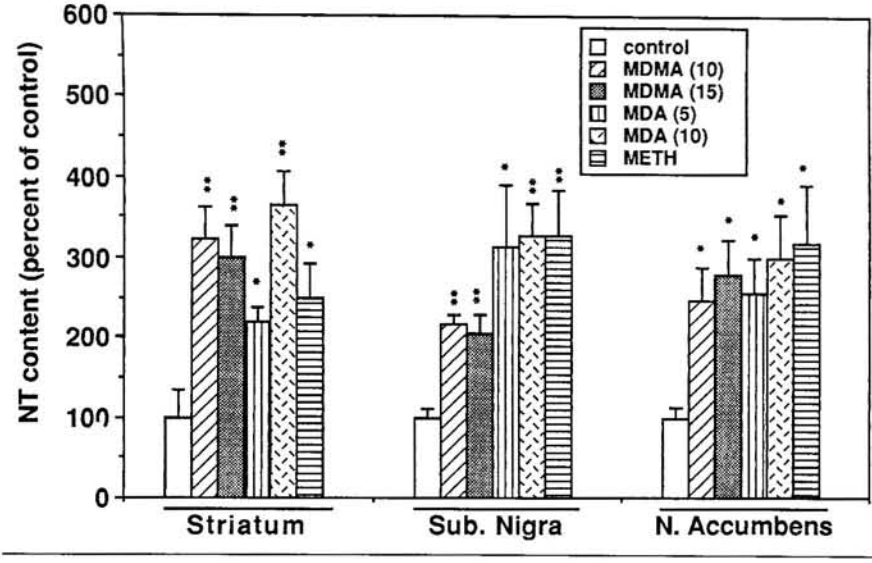

Figure 2. Effects of MDMA, MDA, and methamphetamine on neurotensin levels. Rats received multiple admininstrations of 2 different doses of MDMA (10 or 15 mg/kg/dose) or MDA (5 or 10 mg/kg/dose) or a single dose of METH (15 mg/kg/dose), as described for Figure 1. *$P < 0.01$ and **$P < 0.001$ compared to respective controls.

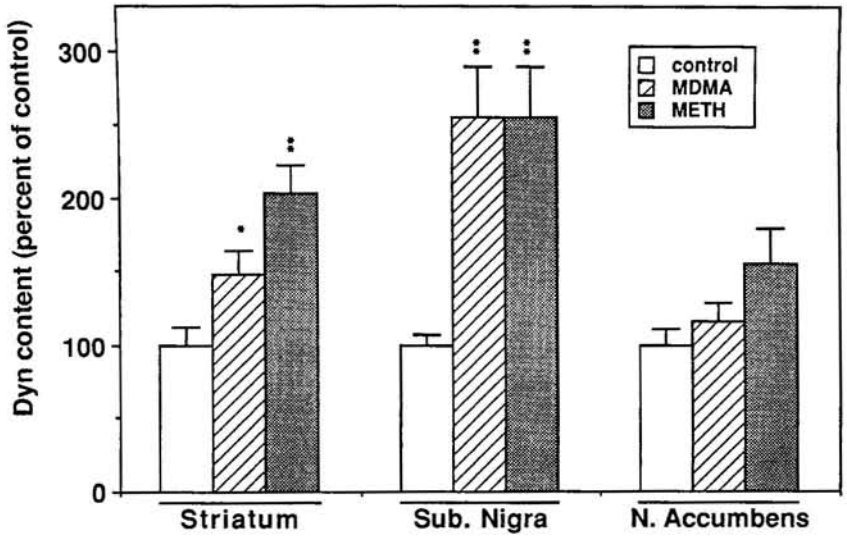

Figure 3. Effect of MDMA and methamphetamine on tissue content of dynorphin A_{1-17}. Rats received multiple administrations of MDMA and METH as described for Figure 1. *$P < 0.05$ and **$P < 0.01$ compared to respective controls.

content in both the striatum and nucleus accumbens than did methamphetamine.

In order to determine how quickly the peptide changes occur in response to MDMA treatment, a single dose of this drug (10 mg/kg) was administered and animals were sacrificed 12 hours later (Figure 4). No significant changes in either striatal or nigral SP content were detected. In contrast, levels of striatal and nigral neurotensin and dynorphin increased from 150% to 400% of controls following the acute MDMA treatments. Although not shown here, similar patterns of peptide responses have been observed after a single dose of methamphetamine [24, 28, 29].

The role of dopamine in mediating the peptide changes after a single MDMA administration was also examined (Figure 5). Selective antagonists for dopamine D-1 (SCH 23390; 0.5 mg/kg) and D-2 (Sulpiride; 80 mg/kg) receptors were administered 15 minutes prior to MDMA injection. The animals were sacrificed 12 hours following treatment, and striata and substantia nigras were removed and analyzed for neurotensin and dynorphin content. In general, blockade of the D-1 receptor totally prevented the MDMA-induced increases in striatal and nigral neurotensin and dynorphin levels. In contrast, the blockade of D-2 receptors did not reduce the MDMA-related changes. In fact, the presence of sulpiride actually enhanced the increase in striatal neurotensin levels caused by MDMA administration. A similar pattern of responses by extrapyramidal neurotensin systems following methamphetamine treatment

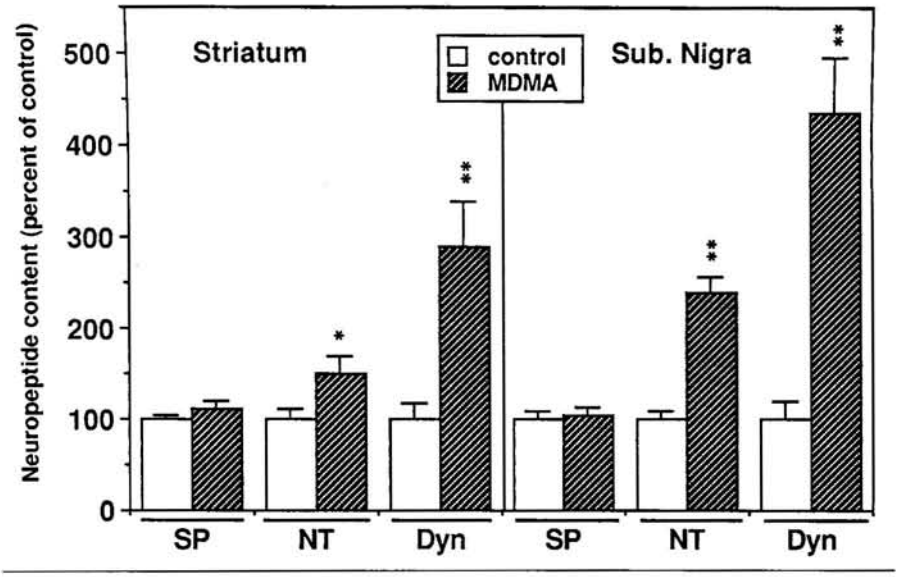

Figure 4. Effect of a single dose of MDMA on neuropeptide levels in extrapyramidal structures. Rats were given a single injection of MDMA (10 mg/kg) and sacrificed 12 hours after treatment. $^{*}P < 0.05$ and $^{**}P < 0.005$ compared to respective controls.

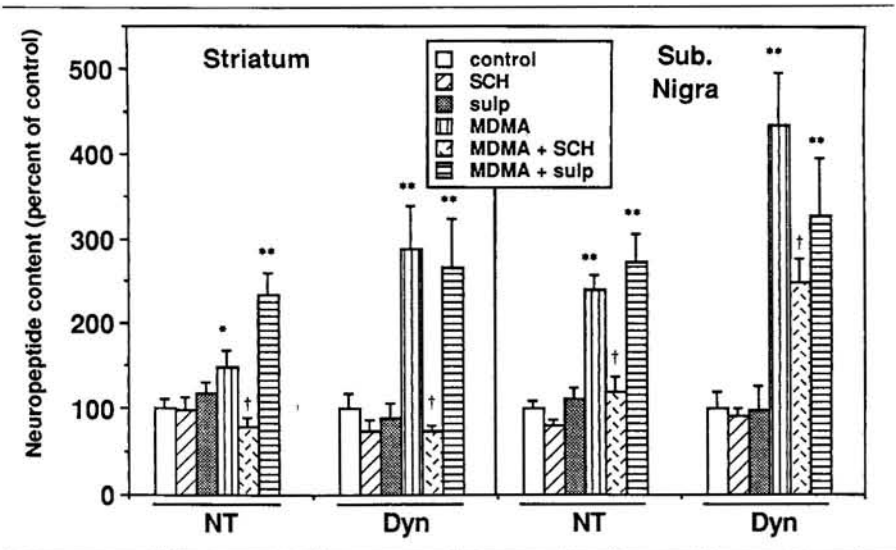

Figure 5. Effects of blockade of dopaminergic D-1 and D-2 receptors on MDMA-induced changes in neurotensin and dynorphin levels. Animals were treated with a single dose of MDMA as described for Figure 4 in the presence or absence of a pretreatment (15 minutes prior) of SCH 23390 (0.5 mg/kg) or sulpiride (80 mg/kg). $^{*}P < 0.05$, $^{**}P < 0.01$ compared to respective controls. $^{\dagger}P \leq 0.05$ compared to corresponding MDMA-treated group.

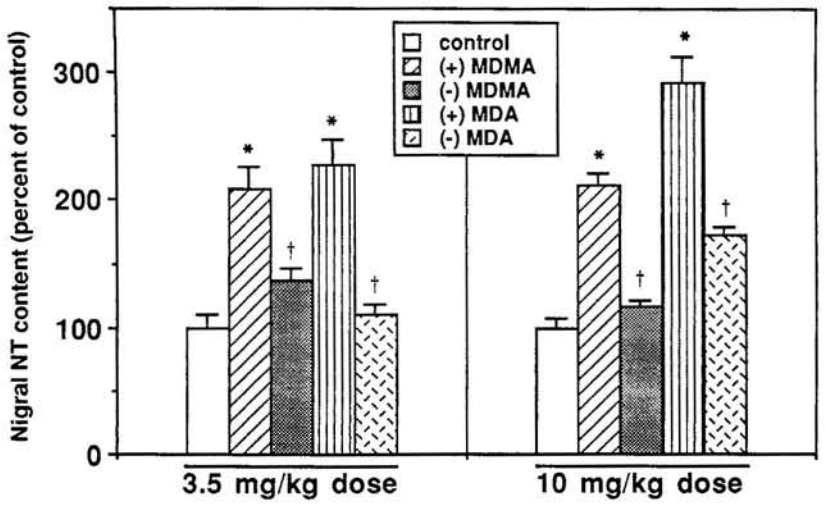

Figure 6. Effects of MDMA isomers on nigral neurotensin levels. Rats received 5 doses of the (+) and (−) isomers of MDMA and MDA according to the treatment schedule described for Figure 1. *$P < 0.01$ compared to corresponding control. †$P < 0.01$ compared to corresponding isomer.

has been reported [27]. One noteworthy exception was the response by the nigral dynorphin system. Antagonism of the D-1 receptor appeared to reduce the MDMA effect only by 50%; D-2 blockade might also have attenuated the MDMA effect, although the change was not statistically significant.

It has been demonstrated by Schmidt and coworkers [5] that the (+) enantiomers of MDMA and MDA are more active on dopaminergic systems than their (−) enantomeric counterparts. Consequently, as the changes in peptide content are likely a result of drug-mediated dopamine release, the effects of two doses of the (+) and (−) enantiomers of both MDMA and MDA were evaluated. Rats received five injections (six-hour intervals between administrations) of 3.5 and 10 mg/kg/dose of both enantiomers of MDMA and MDA. Changes in nigral neurotensin content were determined (Figure 6). For both doses and with both drugs the (+) enantiomer caused a substantially greater increase in nigral neurotensin levels than the corresponding (−) enantiomer.

The effects on neuropeptide systems by one other designer amphetamine was evaluated. Compared to MDMA and MDA, N-ethyl-3,4-methylenedioxyamphetamine (MDE) exerts smaller effects on both the dopaminergic and serotonergic systems, with a quicker recovery [30]. The responses by neurotensin systems of the striatum, substantia nigra, and nucleus accumbens reflected a similar pattern of response (Figure 7). Rats were sacrificed 3 and 18 hours after receiving 5 administrations of 10 mg/kg/dose of MDE. Significant increases in neurotensin content were observed in both the striatum and

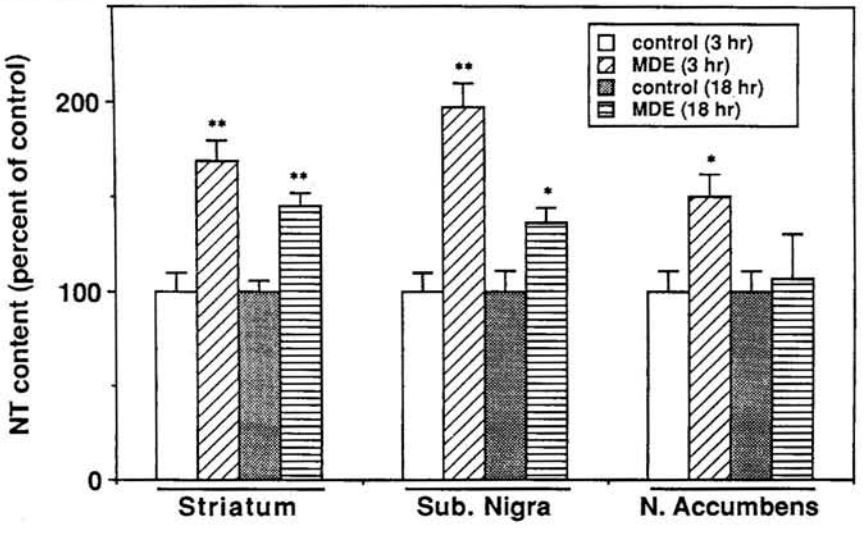

Figure 7. Effects of MDE administration on neurotensin levels. Rats received multiple doses of MDE (10 mg/kg/dose) as described for Figure 1 and animals were sacrificed either 3 or 18 hours following treatment. $^{*}P < 0.02$ and $^{**}P < 0.005$ compared to the corresponding controls.

substantia nigra with the greater increase occurring three hours after treatment. The neurotensin levels were significantly elevated only at the three-hour time in the nucleus accumbens. These data suggest that significant recovery by the neurotensin systems occurs within 18 hours following MDE treatment. Compared with the neurotensin response to similar treatments by MDMA and MDA (Figure 2), MDE was considerably less potent.

These findings demonstrate that at least three peptide systems, specifically SP, neurotensin, and dynorphin pathways in extrapyramidal and limbic structures, are particularly responsive to MDMA, MDA, and, to some extent, MDE administrations. Even a single injection of MDMA caused 150-400% increases in striatal and nigral levels of neurotensin and dynorphin (Figure 4). These peptide changes are almost certainly dopamine-mediated, as coadministration of the D-1 antagonist, SCH 23390, totally blocked or at least substantially attenuated these peptide responses (Figure 5). In addition, those amphetamine analogues that were less potent as dopamine-releasing agents (e.g., MDE less than MDMA and MDA, or (−) isomers less than (+) isomers of MDMA and MDA) caused smaller peptide changes (Figures 6, 7).

For the most part, the effects of MDMA and MDA on the peptides were comparable to those caused by methamphetamine administration (Figures 1,2,3). This finding was somewhat surprising as methamphetamine is thought to have more dopamine-releasing action than either MDMA or MDA [5]. The responses by the peptide systems suggest, in general, that drug-induced in-

creased activity at the dopaminergic postsynaptic receptors (particularly the D-1 subtype) is similar following treatments with methamphetamine, MDMA, and MDA. However, subtle and possibly important differences were observed that may have relevance to the distinctive pharmacological features of each of these drugs. For example, (1) MDMA appeared to be less effective at elevating nigral SP levels than was MDA or methamphetamine (Figure 1); (2) MDMA was only half as effective as MDA or methamphetamine in elevating nigral neurotensin levels (Figures 2,6); and (3) MDMA was less effective than methamphetamine at increasing the levels of dynorphin in the striatum and nucleus accumbens.

The significance of these selective differences is unclear. One possible explanation is that multiple dopaminergic systems are involved in the regulation of the peptide pathways, and these dopamine neuronal networks respond differentially to the designer amphetamines and methamphetamine. Perhaps some dopamine neurons are equally affected by three drugs, thus, the peptide systems linked to these dopaminergic projections are equally influenced by MDMA, MDA, and methamphetamine. However, other dopamine neurons might be more sensitive to the actions of one of the drugs (usually methamphetamine), causing a more dramatic response to treatment with that drug by the peptide systems linked to such dopamine projections. Even so, the present data demonstrate that MDA and MDMA do have an important dopaminergic component to their neurochemical activity, which in some ways appears to be comparable to that of the more traditional amphetamines, such as methamphetamine. Although to a lesser extent, MDE also has significant dopamine-enhancing action.

3. CONCLUSIONS

The significance of the peptide changes in response to drug treatments has not been elucidated. It is possible that decreases in peptide release following treatment with these drugs results in accumulation of the neuropeptides and a rise in peptide tissue content. The dramatic increases in nigral and striatal neurotensin and dynorphin levels following a single dose of MDMA would be suggestive of such a mechanism. Another factor to consider is a drug-induced increase in the synthesis of the peptide. In fact, Bannon et al. [31] have reported that a single dose of methamphetamine causes a substantial rise in the levels of mRNA for preprotachykinin, the SP precursor, suggesting a stimulation of SP synthesis. It is possible that similar drug-induced increases in peptides synthesis are at least a factor in the observed peptide responses.

In order to understand fully the contribution of these peptidergic pathways in mediating the effects of the designer amphetamines, it is necessary to understand their synaptic connections. It is likely that these peptide projections serve at least two major roles. First, they are feedback systems that help to regulate dopaminergic activity, second, they serve an efferent function and transport dopamine-initiated messages to pathways that originate in extra-

pyramidal or limbic structures and project to other brain regions. Consequently, the responses of the peptide systems described herein might be essential in the regulation of feedback phenomena such as drug tolerance and sensitization, as well as serve as important links to conduct drug-induced dopaminergic messages to brain regions crucial for mediating drug effects. As both extrapyramidal and limbic peptidergic pathways appear to be influenced by the designer amphetamines, it is likely that these peptide pathways contribute to the effects of the drugs on locomotion and mental states. These possibilities warrant investigation.

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