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Response of extrapyramidal and limbic neurotensin systems to phencyclidine treatment

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Abstract

Although phencyclidine (PCP) has several neurochemical effects, the most pharmacologically relevant are thought to be its ability to antagonize the activity of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors and to increase extracellular dopamine concentrations. In order to elucidate the nature and consequence of PCP actions on glutamatergic and dopaminergic pathways, this study examined the response of extrapyramidal and limbic neurotensin systems to this drug. Multiple, but not single, doses of PCP caused increases in striatal neurotensin-like immunoreactivity content of 150–200% of control. These effects were blocked by the dopamine D_1 receptor antagonist, SCH 23390, suggesting they were caused by PCP-mediated enhanced dopamine activity at dopamine D_1 receptors. In contrast, MK-801 (dizocilpine), a selective NMDA receptor antagonist that acts at the same site as PCP, had no effect on neurotensin-like immunoreactivity content when given alone. In addition, coadministration of MK-801 with PCP did not alter the effect of PCP on striatal neurotensin-like immunoreactivity content. This lack of effect suggests that the actions of PCP on NMDA receptors was not involved in the neurotensin response. The PCP effect on neurotensin striatal pathways also appeared not to be associated with the dopamine D_2 or γ-aminobutyric acid (GABA) systems: a possible role for the sigma receptor in this effect could not be eliminated. Administration of multiple doses of PCP also affected neurotensin-like immunoreactivity content in the nucleus accumbens (160% compared to control) and frontal cortex (40% compared to control), but not the substantia nigra. The neurotensin effects of PCP are compared to those of another psychotomimetic drug of abuse, methamphetamine.

Keywords: Phencyclidine; Neurotensin; NMDA (*N*-methyl-D-aspartate); Dopamine; Striatum; Nucleus accumbens

1. Introduction

Phencyclidine [*N*-(1-phenylcyclohexyl) piperidine hydrochloride, PCP] is an especially dangerous drug of abuse that possesses potent psychotomimetic properties. Adverse effects caused by PCP use include violent behavior, hallucinations and psychotic states that resemble some forms of schizophrenia (Rao et al., 1990). The pharmacological actions of PCP resemble drugs from several groups including central nervous system (CNS) stimulants, hallucinogens and general anesthetics (Junien and Leonard, 1989). Although the precise mechanisms for these PCP-induced adverse effects are not yet identified, recent studies have demonstrated that this drug interacts with several CNS systems, which include: the haloperidol-sensitive σ receptor, the cholinergic nicotinic receptor, the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor and the dopamine uptake carrier (Rothman et al., 1989). Of these putative action sites, it is hypothesized that the most pharmacologically relevant effects of PCP are to interfere with the Ca^{2+} influx associated with the NMDA-linked Ca^{2+} channel and to increase extracellular dopamine concentration (Rothman et al., 1989). However, the relationship between the effects of PCP on the NMDA and dopamine systems is not fully understood (Rothman et al., 1989; Hondo et al., 1994).

One approach to elucidating the nature and conse-

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quence of PCP action on glutamatergic and dopaminergic pathways is to identify and characterize the response of other associated transmitter systems to PCP administration. For example, a recent report demonstrated that PCP has a profound effect on extrapyramidal and limbic neuropeptide Y neurons. Thus, administration of a single or multiple doses of PCP reduces the concentration of neuropeptide Y-like immunoreactivity in the striatum, nucleus accumbens and frontal cortex by 50% or more. The effects of PCP on these putative neuropeptide transmitter systems are caused principally by blockade of NMDA receptor activity and mediated by γ-aminobutyric acid (GABA) pathways. However, PCP-induced increased activity at dopamine D_1 receptors also appears to contribute to this effect (Midgley et al., 1992; Midgley et al., 1993).

In the present study, the effects of PCP on extrapyramidal and limbic neurotensin systems were investigated. This tridecapeptide is a putative neurotransmitter that has been closely linked to nigral-striatal (Castel et al., 1993), mesolimbic (Tanganelli et al., 1994; Kalivas et al., 1981; Woulfe and Beaudet, 1989), and mesocortical (Merchant et al., 1988; Bean et al., 1989) dopamine pathways. Neurotensin activity is sensitive to changes in dopamine receptor activity in the neostriatum (Letter et al., 1987a; Nemeroff and Cain, 1985), substantia nigra (Hanson et al., 1992), nucleus accumbens and frontal cortex (Merchant et al., 1988; Bean et al., 1989). Consequently, drugs that enhance or antagonize dopamine activity change the tissue concentration of neurotensin-like immunoreactivity. Thus, treatment with methamphetamine causes 200–300% increases in striatal, accumbens and nigra neurotensin-like immunoreactivity levels but approximately a 30–40% decrease in neurotensin-like immunoreactivity content of the frontal cortex. These methamphetamine-induced changes in neurotensin systems are the result of the stimulation of dopamine D_1 receptors as the changes in neurotensin-like immunoreactivity levels are blocked by the selective dopamine D_1 receptor antagonist, SCH23390 (Letter et al., 1987b; Merchant et al., 1988). In addition, blockade of dopamine D_2 receptors also dramatically alters neurotensin activity as treatment with the dopamine D_2 receptor antagonists, haloperidol or sulpiride, increases striatal and accumbens neurotensin-like immunoreactivity concentrations, decreases neurotensin-like immunoreactivity levels in the frontal cortex and has no effect on nigral neurotensin systems (Merchant et al., 1988, 1989, 1990; Govoni et al., 1980; Frey et al., 1986; Myers et al., 1992).

Because of the close association between dopamine and neurotensin pathways, the response of extrapyramidal and limbic neurotensin systems to PCP treatment was evaluated to elucidate the consequences of PCP-induced changes in dopamine activity.

2. Materials and methods

2.1. Animals and treatments

Male Sprague-Dawley rats (180–270 g, Simonsen Laboratories, Gilroy, CA) were maintained in a controlled environment with 12-h light/dark cycles and free access to food and water. Drugs dissolved in 0.9% saline included: phencyclidine-HCl (National Institute on Drug Abuse, Rockville, MD); the dopamine D_1 receptor antagonist, SCH 23390-HCl (Research Biochemicals, Natick, MA); the σ receptor antagonist, rimcazole-HCl (Burroughs Wellcome, Research Triangle Park, NC); the GABA-T (GABA transaminase) suicide inhibitor, γ-vinyl-GABA (GVG, vigabatrin, MDL 71,754; Marion Merrell Dow, Cincinnati, OH: ref. Jung et al., 1977): the NMDA receptor antagonist, MK-801 hydrogen maleate (dizocilpine, Research Biochemicals, Natick, MA). Vehicle for dissolving the dopamine D_2 receptor antagonist, (±)-sulpiride (Sigma Chemical Co., St. Louis, MO) was 2% lactate + 25% propylene glycol-saline. All drugs were administered intraperitoneally with the exception of PCP, which was administered subcutaneously. Those animals administered the GABA-T suicide inhibitor, γ-vinyl-GABA, received two doses (1200 mg/kg per dose) 48 and 1 h prior to challenge. Drug doses, except for MK-801, were calculated as the free base. Control animals received identical treatment regimens using vehicles only.

In acute experiments, animals received a single dose of PCP (15 mg/kg) and were killed 6, 12 and 24 h after drug injection. For multiple dose experiments, animals received five doses of PCP (15 mg/kg per dose; unless otherwise stated), MK-801 (1 mg/kg per dose; unless otherwise stated) or antagonist/agonist 6 h apart and were killed 18 h after treatment or as indicated. All antagonists were given 20 min prior to PCP administration.

2.2. Dissections

All animals were killed by decapitation at the indicated times after treatment. Brains were rapidly removed and placed on ice, striata (caudate-putamen) were excised, and the remaining brain tissues immediately frozen on dry ice and stored at −80°C until assayed for neurotensin-like immunoreactivity. The substantia nigrae were identified according to the atlas of König and Klippel (1963), bilaterally dissected out from 1.0-mm thick frozen coronal slices and stored at −80°C until assayed for neurotensin-like immunoreactivity content.

2.3. Radioimmunoassay

The radioimmunoassays for neurotensin-like immunoreactivity were performed according to the meth-

ods described by Letter et al. (1987a). Tissues were homogenized in 0.01 N HCl (proteins were measured according to the method of Bradford, 1976), heated and centrifuged, after which the supernatant was removed, lyophilized and stored at −80°C until assayed. The samples were reconstituted in phosphate-buffered saline plus gelatin. Duplicate aliquots were mixed with the selective neurotensin antisera as previously described (Letter et al., 1987a) and ^{125}I-neurotensin (New England Nuclear, Wilmington, DE). The mixture was incubated at 4°C for 48 h. Antibody-bound and free ^{125}I-labeled peptide were separated by mixing the reactant with a dextran-coated charcoal slurry. Quantities of neurotensin-like immunoreactivity were determined by comparing bound to free ^{125}I-labeled peptide in each sample to a standard curve.

2.4. Statistical analysis

To facilitate comparisons between groups, results in all figures are shown as percentages of respective controls. The control values in neurotensin-like immunoreactivity pg/mg protein are included in the figure legends. Columns represent the mean of treatment groups ± S.E.M. Data were analyzed using a one-factor ANOVA (analysis of variance); if the F ratio was significant, a Fischer PLSD (protected least significant difference) test was used to compare differences between the means of individual groups. Differences were considered significant when the probability that they were zero was less than 5%.

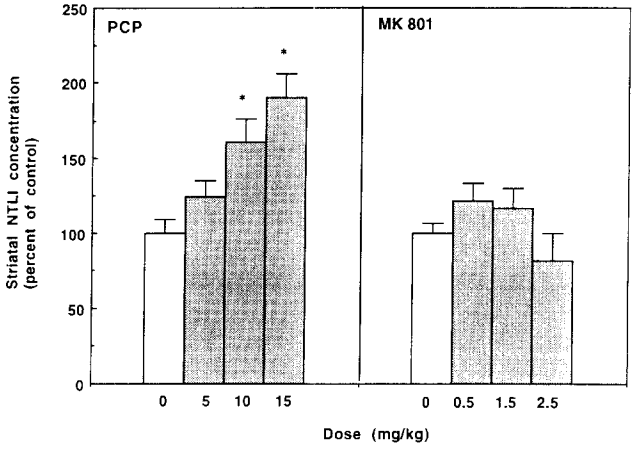

Fig. 1. Effects of multiple administrations of various doses of PCP on striatal neurotensin-like immunoreactivity (NTLI) content. Rats were given five doses of PCP (5, 10 or 15 mg/kg per dose) at 6-h intervals and killed 18 h after the final administration. Results are expressed as percent of control ±S.E.M. ($n = 6$–8). The average value for control neurotensin-like immunoreactivity levels was 127±8 pg/mg protein. $^{*}P < 0.05$ vs. control.

3. Results

3.1. Dose-dependent effect of PCP and MK801 on striatal neurotensin-like immunoreactivity concentrations

The effect of PCP administration on the concentration of neurotensin-like immunoreactivity content in the neostriatum was assessed after multiple injections (five doses at 6-h intervals) of 5, 10 or 15 mg/kg of PCP to Sprague Dawley rats (Fig. 1). The striatal levels of neurotensin-like immunoreactivity were significantly elevated in a dose-dependent fashion after 10 (161% of control) and 15 (190% of control) mg/kg per dose. In order to determine if this neurotensin effect was due to blockade of the NMDA-linked Ca^{2+} channel, another drug with PCP-like channel-blocking properties (MK-801), was also administered in a similar dose-dependent fashion (Fig. 1). Unlike PCP, MK-801 did not significantly alter striatal neurotensin-like immunoreactivity levels at any of the doses examined.

3.2. The time-dependent response of striatal neurotensin systems to single and multiple doses of PCP

In order to characterize the response of striatal neurotensin systems to the effects of PCP, 15 mg/kg of this drug was administered as a single or multiple (5 times) doses. After a single injection of drug, animals were killed 6, 12 or 24 h later, while animals receiving multiple PCP administrations were killed 10, 18, 34 or 54 h after treatment. Striatal levels of neurotensin-like immunoreactivity were not significantly altered after any of the time points examined in animals receiving a single dose (Fig. 2A), suggesting more than one administration of PCP is required to cause the response in striatal *NT* systems. In contrast, significant increases in striatal neurotensin-like immunoreactivity concentration were observed at 10, 18 and 34 h after multiple dose treatment, but the striatal content of this neuropeptide returned to control after 58 h (Fig. 2B). These data confirm the neurotensin response to multiple doses of PCP presented in Fig. 1 and demonstrate that it persists for at least 34 h; however, the observation that neurotensin-like immunoreactivity levels eventually return to control demonstrates that the effect is temporary.

3.3. The nature of the PCP-induced change in the striatal neurotensin system

Multiple doses (15 mg/kg per dose) of PCP were administered as described for Fig. 1 with or without other drugs that selectively: (1) blocked dopamine D_1 (SCH 23390; SCH) or dopamine D_2 (sulpiride; sulp) receptors, (2) altered σ receptors (rimcazole; rim), (3) enhanced GABA levels (γ-vinyl GABA; GVG), or (4)

blocked the NMDA-linked Ca^{2+}-channel (MK-801). The results of these treatments are presented in Fig. 3 and reveal that, as shown in Figs. 1 and 2, the PCP treatment elevated striatal neurotensin-like immunoreactivity levels. The only other single drug treatment that also had a significant effect on neurotensin-like immunoreactivity content was sulpiride. As reported by several groups, blockade of dopamine D_2 receptors significantly increases striatal neurotensin-like immunoreactivity (Merchant et al., 1988; Frey et al., 1986; Myers et al., 1992). In PCP-treated animals receiving other drugs, only the coadministration of SCH 23390 completely blocked the response of the striatal neurotensin system to PCP; however, the presence of the σ receptor-directed drug, rimcazole, may have had some attenuating effect. In contrast, blockade of the

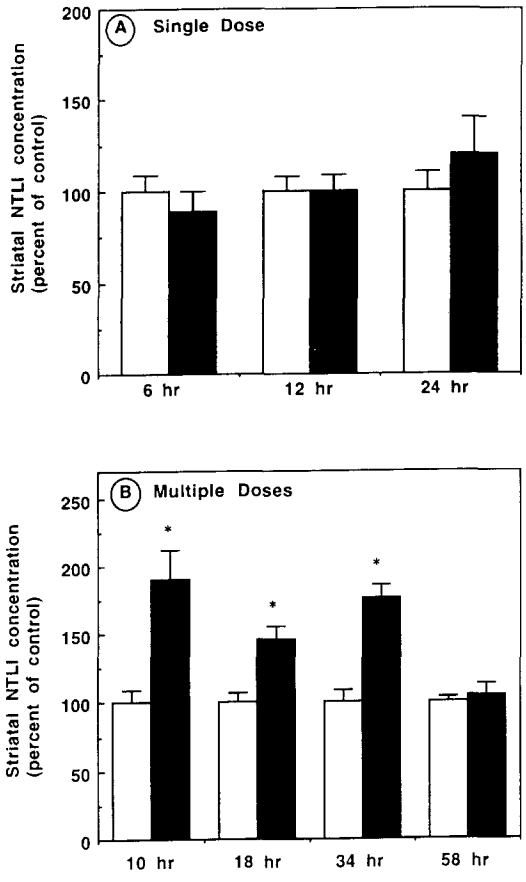

Fig. 2. Effects of single and multiple PCP administrations on striatal neurotensin-like immunoreactivity (NTLI) content. (A) Rats were given a single dose of PCP (15 mg/kg) and killed; 6, 12 or 24 h after injection. The average value for control neurotensin-like immunoreactivity levels was 92 ± 8 pg/mg protein. (B) Rats were administered five doses of PCP (15 mg/kg per dose) 6 h apart and sacrificed 10, 18, 34 or 58 h after the final dose. Average control value for neurotensin-like immunoreactivity levels was 111 ± 10 pg/mg protein. $^{*}P < 0.05$ vs. respective controls. Results shown in both panels are expressed as percent of respective controls $\pm$ S.E.M. ($n = 6$). Controls are open columns and PCP-treated groups are darkened columns.

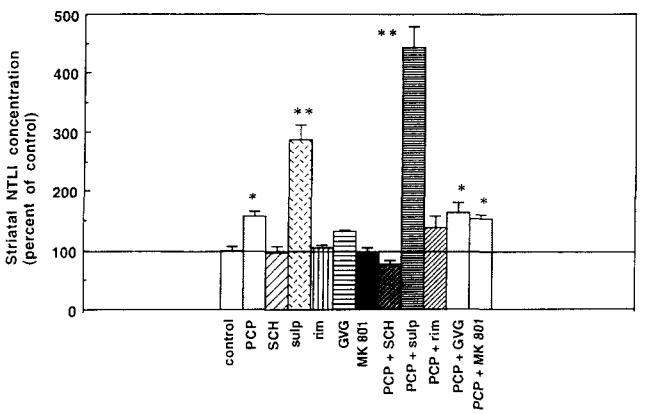

Fig. 3. Effects on PCP-induced changes in striatal neurotensin-like immunoreactivity (NTLI) content of dopamine D_1 and D_2 receptor blockade, sigma receptor alteration, increased GABA levels, and MK-801 coadministration. Rats were treated with SCH 23390 (SCH; 0.5 mg/kg per dose), sulpiride (sulp; 80 mg/kg per dose), rimcazole (rim; 12.5 mg/kg per dose), GVG (as described in Materials and methods) or MK-801 (1.0 mg/kg per dose) alone or in combination with PCP (15 mg/kg per dose). Average control value for striatal neurotensin-like immunoreactivity concentration was 128 ± 10 pg/mg protein. Rats were killed 15–18 h after treatment. Values are expressed as percent of control $\pm$ S.E.M. ($n = 6$). $^{*}P < 0.05$ vs. control; $^{**}P < 0.05$ vs. all other values.

dopamine D_2 receptor by sulpiride, in the presence of PCP, resulted in an enhanced response; i.e., the combination treatment increased striatal neurotensin-like immunoreactivity concentration to 444% of control compared to increases of 165% and 287% of control caused by PCP and sulpiride treatments, respectively.

3.4. Effects of multiple doses of PCP on neurotensin systems associated with the substantia nigra and limbic structures.

The effects of PCP multiple-dose treatment on non-striatal structures were determined in rats receiving the PCP treatment described for Fig. 1. 18 h after treatment, the neurotensin-like immunoreactivity content in substantia nigra and the limbic regions of the frontal cortex and nucleus accumbens was measured. The frontal cortex and nucleus accumbens were evaluated because, like the neostriatum, these two brain regions have neurotensin systems associated with the neuronal terminals of dopamine pathways (Tanganelli et al., 1994; Bean et al., 1989). PCP treatment increased the accumbens neurotensin-like immunoreactivity concentration in a manner similar to that observed in the striatum (compare Figs. 1 and 4); however, in contrast, the neurotensin-like immunoreactivity content of the frontal cortex was substantially decreased to 40% of control (Fig. 4). In order to assess the response of neurotensin systems associated with dopamine neuronal cell bodies, neurotensin-like immunoreactivity

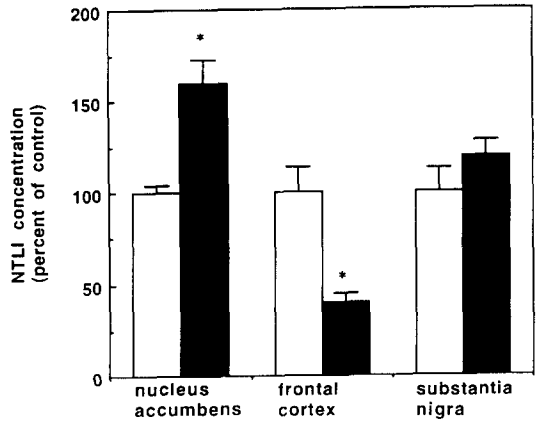

Fig. 4. Effects of multiple doses of PCP on neurotensin-like immunoreactivity (NTLI) content in limbic structures and the substantia nigra. Five doses of PCP (15 mg/kg per dose) were administered as described for Fig. 1. The effects of PCP treatment on neurotensin-like immunoreactivity content were determined in the nucleus accumbens, frontal cortex and substantia nigra. Results are expressed as percent of respective controls ± S.E.M. ($n = 6$). The average neurotensin-like immunoreactivity content values for nucleus accumbens, frontal cortex and substantia nigra were 732 ± 30, 32 ± 4 and 448 ± 58 pg/mg protein. $^{*}P < 0.05$ vs. respective controls.

content of the substantia nigra was assessed (Castel et al., 1993). Unlike the other brain regions examined in this study, multiple doses of PCP did not significantly alter nigral neurotensin-like immunoreactivity content (Fig. 4).

4. Discussion

These findings demonstrate that neurotensin-related systems in both extrapyramidal and limbic structures are altered by multiple exposures to PCP. It is noteworthy that the affected brain regions examined in this study include neuronal terminals associated with dopaminergic pathways. The activity of these neurotensin systems is altered by changes in dopamine activity (Nemeroff and Cain, 1985; Merchant et al., 1988, 1989; Letter et al., 1987a, Myers et al., 1992; Hanson et al., 1992). This is consistent with the observation that the PCP-induced changes in neurotensin-like immunoreactivity content are mediated primarily by activation of dopamine D_1 receptors (Fig. 3): such an effect is likely the consequence of PCP-induced increases in extracellular dopamine (Maurice et al., 1991; Steinpreis and Salamone, 1993).

For this initial study, the entire neostriatum was used to demonstrate that PCP altered neurotensin activity (Figs. 1 and 2) and to elucidate the mechanism of this effect (Fig. 3). Because Gygi et al. (1994) demonstrated that neurotensin systems of various caudate regions and the globus pallidus have unique responses to psychotomimetic drugs such as methamphetamine and cocaine, it is possible that PCP also differentially affects neurotensin systems according to their neostriatal location. Although the anatomical features of the neostriatal effect by PCP was not fully characterized in this study, in a separate experiment we did observe that multiple doses of 15 mg/kg PCP (as described for Fig. 1) did cause significant increases in neurotensin-like immunoreactivity content in the medial (182% of control) and lateral (194% of control) anterior caudate (1–2 mm rostral to bregma) but did not alter neurotensin-like immunoreactivity levels in the very anterior caudate (2–3 mm rostral to bregma) nor in the globus pallidus. These preliminary findings suggest the presence of multiple neurotensin systems in the neostriatum, some of which are affected by PCP and some are not.

The significance of the changes in neurotensin systems is presently unclear, although this neuropeptide is thought to help regulate extrapyramidal motor activity and limbic-associated mental states (Nemeroff and Cain, 1985; Castel et al., 1993). Because PCP use clearly influences such CNS functions, perhaps these neurotensin changes are involved. The lack of a neurotensin effect by MK-801 treatment suggests that the actions of PCP on NMDA receptors do not contribute to the changes in neurotensin systems. Although the results clearly demonstrate that the neurotensin response to PCP is principally mediated by activation of dopamine D_1 receptors, other transmitter systems may also contribute. For example, the role of sigma receptors in this neurotensin effect is not clear. PCP has affinity for the σ receptor (Junien and Leonard, 1989) and the coadministration of the sigma receptor directed drug, rimcazole, may have influenced the PCP effect (Fig. 3) suggesting that this receptor may play some role in mediating the striatal neurotensin response to PCP.

Although PCP-induced changes in neurotensin-like immunoreactivity tissue concentration suggest that this drug alters the function of neurotensin pathways, it is not clear how their activity was affected. Thus, increases in neurotensin-like immunoreactivity content could be caused by reduced release and turnover of this peptide resulting in its accumulation in neuronal terminals. Another possibility is that neurotensin levels increase due to a stimulation of its synthesis. Which, if either, of these mechanisms accounts for the increases in neurotensin-like immunoreactivity tissue levels can not be determined from the current data. However, similar increases in striatal and accumbens neurotensin-like immunoreactivity concentrations caused by methamphetamine are associated with increases in

neurotensin mRNA in the nucleus accumbens and ventral striatum (Merchant et al., 1994). The similarity with the methamphetamine effects suggests that PCP also likely stimulates neurotensin synthesis. As of yet, the effects of these drugs on neurotensin release have not yet been studied.

As mentioned, PCP and stimulants such as methamphetamine, have some pharmacological similarities. Both drugs increase extracellular dopamine, cause agitation and psychotic behavior (often with schizophrenia-like symptoms) and are euphorigenic (Hondo et al., 1994). Our study demonstrates that similarities also exist in the manner extrapyramidal and limbic neurotensin systems respond to PCP and methamphetamine, thus: (1) multiple doses of both drugs increase neurotensin-like immunoreactivity concentration in the striatum, nucleus accumbens and decrease neurotensin-like immunoreactivity levels in the frontal cortex (Figs. 1, 2 and 4; Letter et al., 1987a; Merchant et al., 1988); (2) the effects of both drugs on neurotensin are completely blocked by dopamine D_1 receptor antagonists (Fig. 3; Hanson et al., 1992; Merchant et al., 1988);(3) the neurotensin response to both drugs is additive or synergistic with the increase in striatal neurotensin-like immunoreactivity levels caused by blockade of dopamine D_2 receptors (Fig. 3; Letter et al., 1987b). However, there are also significant differences in the pharmacology of PCP and methamphetamine. For example, the psychotic behavior caused by PCP, but not methamphetamine, often includes the deficit symptoms, such as flattened affect and 'negative' symptomology of some forms of schizophrenia (Steinpreis et al., 1994). Our findings also revealed differences in the way neurotensin systems respond to these two drugs. Firstly, no significant changes in striatal neurotensin systems were observed up to 24 h following an acute PCP treatment (Fig. 2) while a single dose of methamphetamine increases neurotensin-like immunoreactivity content as soon as 6 h after treatment (Letter et al., 1987a). Secondly, nigral neurotensin-like immunoreactivity levels are unaffected after multiple PCP administrations (Fig. 4) while methamphetamine substantially increases nigral neurotensin-like immunoreactivity content (Letter et al., 1987a). Finally, although the methamphetamine-induced neurotensin changes are principally mediated by dopamine D_1 receptors, they are also prevented when NMDA receptor activity is blocked by the channel blocker, MK-801, (Singh, et al., 1990); in contrast, MK-801 had no apparent effect on PCP-induced increases in striatal neurotensin-like immunoreactivity levels (Fig. 3). Thus, in contrast to methamphetamine, the neurotensin response to PCP is independent of the NMDA system.

PCP dramatically affects extrapyramidal and limbic neuropeptide systems other than neurotensin pathways. As previously discussed, a recent report demonstrates that PCP treatment causes changes in the tissue levels of neuropeptide Y-like immunoreactivity. Comparisons between the neurotensin and neuropeptide Y responses reveal similarities that include: (1) multiple PCP doses affect both neuropeptide systems in a similar temporal fashion (Figs. 1 and 2; Midgley et al., 1992) and (2) changes in neurotensin-like and neuropeptide Y-like immunoreactivity levels occur in the striatum, nucleus accumbens and frontal cortex, but not in the substantia nigra (Fig. 4; Midgley et al., 1992). However, differential responses by neurotensin and neuropeptide Y pathways to PCP demonstrate that distinct mechanisms account for the impact of this drug on these two neuropeptide systems. For example, while PCP treatment increased neurotensin-like immunoreactivity tissue levels, the same treatments decreased neuropeptide Y-like immunoreactivity content. In addition, a single PCP dose caused a significant decrease in striatal neuropeptide Y-like immunoreactivity levels after 12 h (Midgley et al., 1992), but did not affect neurotensin-like immunoreactivity concentration at any time examined (Fig. 2). Another important difference is that contrary to the neurotensin effects, the neuropeptide Y changes are due principally to the ability of PCP to block NMDA receptor activity; thus, MK-801 caused PCP-like decreases in neuropeptide Y-like immunoreactivity levels (Midgley et al., 1992), but had no effect on neurotensin-like immunoreactivity tissue content (Fig. 1). Finally, GABA has an important role in the PCP-induced striatal neuropeptide Y changes as these effects are completely blocked by a GABA-enhancing drug like γ-vinyl-GABA (Midgley et al., 1992); in distinction, the neurotensin changes in response to PCP were not significantly influenced by the coadministration of this GABA-transaminase inhibitor (Fig. 3).

In summary, the illicit psychotomimetic PCP has profound effects on extrapyramidal and limbic neurotensin systems. These effects are likely due to enhanced dopamine activity at dopamine D_1 receptors but independent of PCP-related NMDA receptor antagonism in these brain regions. The neurotensin changes caused by methamphetamine appear to have some similarities as well as differences to the PCP effects. A possible explanation is that while both drugs increase extracellular dopamine concentration, perhaps they mediate this effect by different mechanisms and/or activate different dopamine pathways, resulting in differences in the neurotensin responses. A comparison with the neuropeptide Y systems reveals that effects of PCP on NMDA receptors influence the activity of this neuropeptide in the same tissues, but in an opposite direction to the neurotensin changes and by GABA-related mechanisms. The significance of these differential neuropeptide responses to the varied PCP mechanisms needs to be elucidated.

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