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Opposite modulation of apomorphine- or amphetamine-induced stereotypy by antagonists of CCK receptors

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Abstract

Stereotyped behavior is elicited by activation of dopaminergic systems with drugs such as apomorphine and amphetamine. In previous studies, we have reported that the sulfated cholecystokinin octapeptide (CCK-8) decreased apomorphine-induced stereotypy in animals with normal and supersensitive dopamine receptors. The aim of the present study was to evaluate the effects of CCK_1 and CCK_2 receptor antagonists on stereotyped behavior induced by apomorphine or amphetamine. Rats were pretreated with the CCK_1 (SR 27897B; 1-[[2-(4-(2-chlorophenyl) thiazol-2-yl) aminocarbonyl]indolyl]acetic acid; 500 μg/kg; i.p.) or CCK_2 (L-365,260; 3R-(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5 phenyl-1*H*-1,4-benzodiazepine-3-yl)-*N*′-(3-methyl phenyl)-urea; 500 μg/kg; i.p.) receptor antagonists or saline 15 min before apomorphine (0.6 mg/kg; s.c.) or amphetamine (9.0 mg/kg; i.p.) injection. Both CCK_1 and CCK_2 receptor antagonists significantly increased apomorphine-induced stereotypy. In contrast, only the blockade of CCK_2 receptors significantly decreased amphetamine-induced stereotypy. The results suggest a dual opposite mechanism for CCK–dopamine interactions. These data also suggest that both apomorphine- and amphetamine-induced stereotypy should be used whenever effects of drugs acting on dopaminergic systems are being assessed.

Keywords: SR 27897B; L-365,260; Cholecystokinin; Dopamine; CCK_A receptor; CCK_B receptor

1. Introduction

It is well known that dopaminergic over-stimulation leads to stereotyped behavior in different species. This behavior can be induced by the dopamine receptor agonist apomorphine (Ljunberg and Ungerstedt, 1977, 1978) or by the dopamine-releasing agent amphetamine (Robbins, 1978). The effects are dose-dependent in both cases (Felicio et al., 1987; Mueller and Whiteside, 1990; Clark et al., 1991; Kihara et al., 1993). The main components of stereotypy differ both in qualitative and quantitative terms depending on the drug used to elicit the phenomenon (Fray et al., 1980). These differences have been well described by Antoniou and Kafetzopoulos (1991), who also showed that the components of stereotyped behavior are diversely modified by striatal lesions (Antoniou and Kafetzopoulos, 1992).

In humans, stereotypy occurs during both boring and stressful situations (Dourish and Cooper, 1990). Stereotyped behavior is also known to occur in a large number of neurological and psychiatric disorders such as Parkinson's disease, Huntington's Chorea, autism, schizophrenia and Gilles de la Tourette syndrome and for this reason, the study of stereotyped behavior has become an important tool in behavioral pharmacology (Ellenbroek and Cools, 1993).

Since 1980 when Hökfelt et al. described the existence of cholecystokinin (CCK) in mesencephalic dopaminergic neurons, there has been an increasing interest in this peptide family. There is abundant CCK in the brain. Its distribution is uneven but is similar in humans, pigs,

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guinea pigs and rats. CCK is present in neurons in the cortex, basal ganglia, hippocampus, septum, amygdala, mesencephalon, hypothalamus and spinal cord (Moran and McHugh, 1990), where it appears as sulphated cholecystokinin octapeptide (CCK-8) and, to a lesser extent, as cholecystokinin tetrapeptide (CCK-4).

There are two CCK receptor subtypes, CCK_1 and CCK_2 (previously named CCK_A and CCK_B) (Alexander and Peters, 1998). They have wide distribution and countless functions and support pharmacological heterogeneity (Wank, 1995). Binding and autoradiography studies have detected CCK_1 receptors in high concentration throughout the gastrointestinal tract and in a few discrete brain regions such as the area postrema, nucleus of the solitary tract, interpeduncular nucleus, dorsal raphe, nucleus accumbens, substantia nigra and ventral tegmental area. CCK_2 receptors are mainly distributed in the brain, with the highest concentration in the striatum, cerebral cortex and limbic system, but they can also be found in the stomach (Roques and Noble, 1998). Two affinity states with different functions have been also described for CCK_2 (Léna et al., 1997) and radioligand binding assays suggest the existence of two CCK_2 receptor subtypes (Harper et al., 1996). CCK-8 has about the same affinity for both receptors, while CCK-4 shows very low affinity for the CCK_1 receptor and the same affinity as CCK-8 for the CCK_2 receptor (Crawley, 1991). Several selective nonpeptide receptor antagonists have been developed and widely used in pharmacological studies, like SR 27897B and L-365,260, which are specific for CCK_1 and CCK_2 receptors, respectively (Ding and Hakanson, 1996; Zajac et al., 1996; Betancur et al., 1997). Both of them reach the brain and have different kind of effects in the central nervous system when injected peripherally (Poncelet et al., 1993; Josselyn et al., 1997; Ladurelle et al., 1998; Bignon et al., 1999; Miranda-Paiva and Felicio, 1999).

The most important anatomical regions of the brain involved in stereotypy are the nucleus accumbens (Weiss et al., 1988; Kokkinidis et al., 1989) and the caudate–putamen nucleus (Kokkinidis et al., 1989; Antoniou and Kafetzopoulos, 1992). CCK and dopamine are present in both areas. They coexist in the medial posterior nucleus accumbens but are not in the same synapses in the anterior nucleus accumbens or in the caudate–putamen nucleus (Crawley, 1994). Intrinsic and extrinsic CCK systems have been reported to be present in the rat striatum (Hökfelt et al., 1988); the extrinsic system originates from the mesencephalon (Hökfelt et al., 1980) and telencenphalon (Meyer and Krauss, 1983; Morino et al., 1992). In addition, there is evidence that subpopulations of nigrostriatal dopaminergic neurons contain CCK-8 as a co-transmitter (Hökfelt et al., 1980) and that glutamate and CCK coexist in corticostriatal systems (You et al., 1994).

The influence of CCK on dopamine-mediated behaviors has been extensively studied. Apomorphine-induced stereotypy is decreased by intracerebroventricular injections of CCK both in normal and supersensitive rats (Tieppo et al., 1995, 1997). Both i.p. and s.c. CCK treatment decreased apomorphine-induced stereotypy and the avoidance response in a dose-dependent manner but failed to produce catalepsy in vertical grip tests. These data suggest that peripherally administered CCK has neuroleptic-like effects (Cohen et al., 1982). When the CCK receptor agonist ceruletide was injected in mice, an antistereotypic effect was also described (Zetler, 1986). Locomotor activity in rodents was reduced by CCK-8 treatment and this effect was dose-dependently antagonized by the CCK_1 receptor antagonists (Soar et al., 1989; O'Neill et al., 1991; Hirosue et al., 1992; Poncelet et al., 1993). CCK-8 injected into the nucleus accumbens attenuates the supersensitive locomotor response to apomorphine in 6-hidroxidopamine and chronic–neuroleptic treated rats (Weiss et al., 1989). In mice, orally administered CCK_1 receptor agonist reduced locomotor activity and intrastriatally administered CCK_1 receptor agonist elicited contralateral turning behavior. Both effects were prevented by SR-27897B (Bignon et al., 1999). In a strain of rats lacking CCK_1 receptors, hypolocomotion and a decrease in the incidence of rearing were observed in open-field tests (Kobayashi et al., 1996). Ceruletide, a CCK analog, suppressed apomorphine-induced rotational behavior in 6-hydroxydopamine- lesioned rats via CCK_1 receptors (Fujisawa et al., 1993). The apomorphine-induced hypomotility, a pre-synaptic effect, is abolished by intracerebroventricular CCK injections (Katsuura et al., 1984). CCK-4 reduced SKF 38393 (a dopamine D_1 receptor agonist)-induced grooming and pretreatment with either devazepide (CCK_1 receptor antagonist) or L-365,260 attenuated this effect (van Kampen and Stoessl, 1997). CCK potentiation of apomorphine-induced behaviors has also been described (Worms et al., 1986; Blumstein et al., 1987).

On the other hand, Weiss et al. (1988) demonstrated that both intracerebroventricular and intra-accumbens CCK-8 injections enhanced amphetamine-induced stereo-

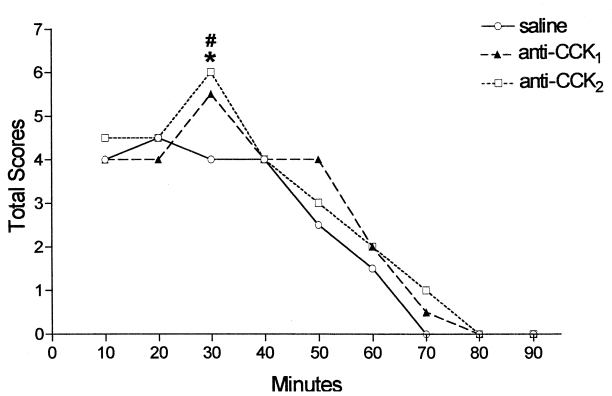

Fig. 1. Time course of apomorphine-induced stereotypy scores (0.6 mg/kg, s.c.). Rats groups were treated i.p. with saline (○–○, $n=14$), SR 27897B (▲–▲, $n=14$) or L-365,260 (□–□, $n=14$) 15 min prior to the behavioral test. Data are medians ± SEM. $^{*}P<0.05$ SR 27897B vs. saline. $^{\#}P<0.05$ L-365,260 vs. saline (for P values, see Results).

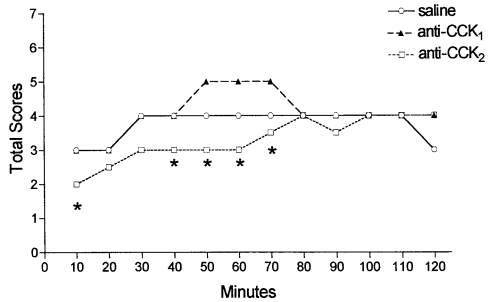

Fig. 2. Time course of amphetamine-induced stereotypy scores (9.0 mg/kg, i.p.). Rat groups were treated i.p. with saline (○–○, $n=13$), SR 27897B (▲–▲, $n=13$) or L-365,260 (□–□, $n=10$) 15 min prior to the behavioral test. Data are means ± SEM. $^{*}P<0.05$ vs. saline (for P values, see Results).

typy, as also reported by others (Crawley et al., 1985). Intra-accumbens CCK enhances amphetamine-induced locomotor stereotypy (Mueller and Whiteside, 1990) as well as amphetamine- and dopamine-induced locomotion (Crawley, 1991). Devazepide did not affect amphetamine-induced locomotion although it blocked the augmented response to subsequent amphetamine challenge after chronic amphetamine treatment (De Sousa et al., 1999). A $CCK_{1/2}$ receptors agonist but not a CCK_2 receptor agonist had a neuroleptic-like profile both in a behavioral test with strong predictive validity for antipsychotic drug activity and in amphetamine-induced hyperlocomotion (Feifel et al., 1999). All of these results further characterize the modulatory action of CCK on the dopamine system.

Although the above data suggest that CCK enhances amphetamine-induced behaviors and decreases apomorphine-induced behaviors, a real controversy remains since the data are not always consistent. The purpose of the present study was to address some of the possible mechanisms involved in CCK–dopamine interaction in stereotyped behavior by assessing the effects of specific CCK_1 and CCK_2 receptor antagonists on this behavior elicited by amphetamine or apomorphine.

2. Materials and methods

2.1. Animals

Seventy-eight adult male rats of Wistar origin, weighing 200–280 g, were used. The animals were kept under a controlled 12 h light–dark cycle (lights on at 0600 h) with food and water available ad libitum throughout the experiment. Animals used in this study were maintained in accordance with the guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council, USA.

2.2. Drugs

The following drugs were used in the present study: apomorphine chlorhydrate (Merck), DL-amphetamine (Sigma), SR 27897B (anti-CCK_1; 1-[[2-(4-(2-chlorophenyl) thiazol-2-yl) aminocarbonyl]indolyl]acetic acid; Sanofi; batch no. 91-01), and L-365,260 (anti-CCK_2; 3R-

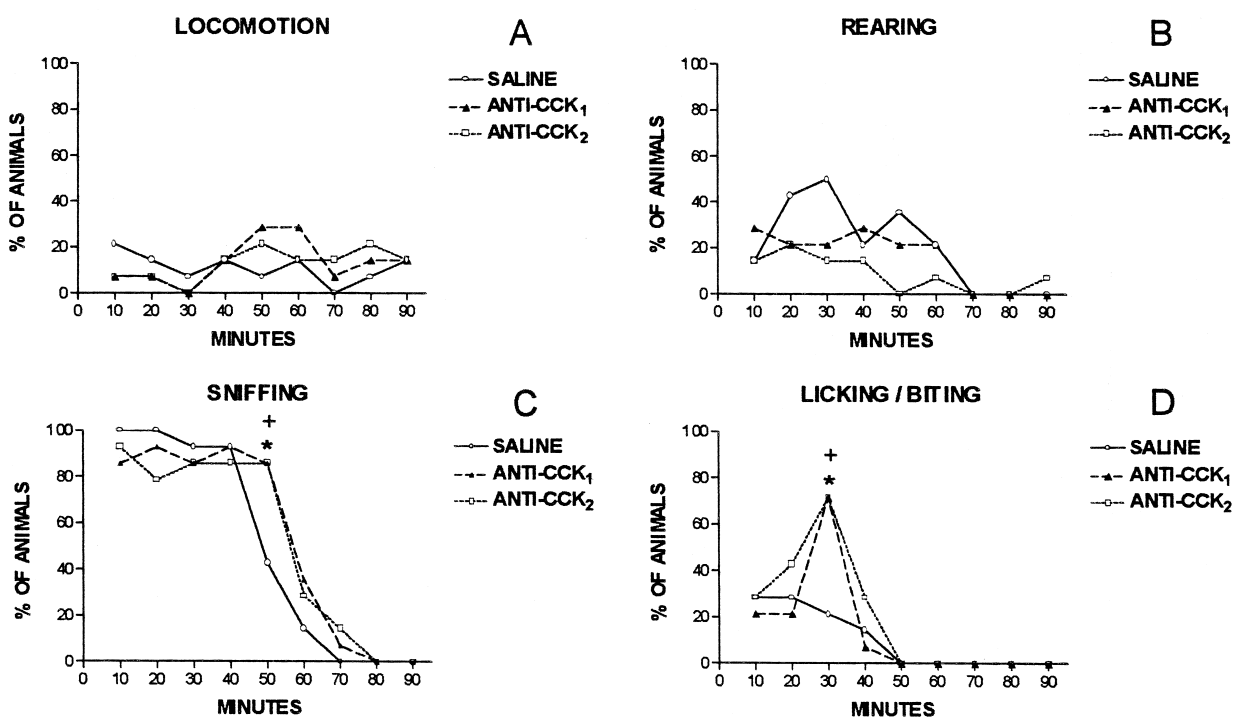

Fig. 3. Time course of Fray's method analysis of apomorphine-induced behavior (0,6 mg/kg). Groups are rats treated i.p. with saline (○–○, $n=13$), SR 27897B (▲–▲, $n=13$) or L-365,260 (□–□, $n=10$) 15 min prior to the behavioral test. Data are percentage of animals that showed the respective behavior. $^{*}P<0.05$ L-365,260 vs. saline. $^{\#}P<0.05$ SR 27897B vs. saline (for P values, see Results).

(+)-*N*-(2,3-dihydro-1-methyl-2-oxo-5 phenyl-1*H*-1,4-benzodiazepine-3-yl)-*N*′-(3-methyl phenyl)-urea; Merck). Apomorphine and DL-amphetamine were prepared in saline. SR 27897B and L-365,260 were made soluble in saline by adding one to two drops of Tween-85. Saline was the control injection for the CCK receptor antagonists.

2.3. Experimental procedure

Fifteen minutes before the behavioral test, animals were pretreated i.p. with SR 27897B (a CCK_1 receptor antagonist, 500 μg/kg), L-365,260 (a CCK_2 receptor antagonist, 500 μg/kg, i.p.) or saline. For the behavioral test, apomorphine (0.6 mg/kg, s.c.)- or amphetamine (9.0 mg/kg, i.p.)-induced stereotyped behavior was evaluated in experiments 1 and 2, respectively. The apomorphine dose was the same as used in previous studies (Tieppo et al., 1995, 1997). After a preliminary experiment in which a dose–response curve for amphetamine was constructed with doses ranging from 5 to 9 mg/kg i.p., the amphetamine dose was chosen to elicit a behavioral expression of the same magnitude as that shown by apomorphine. Stereotypy was quantified every 10 min for 90 min or 120 min immediately after apomorphine or amphetamine treatment, respectively, which are intervals that permit to observe the whole course of time of apomorphine behavioral effects and amphetamine effects at times comparable with those for apomorphine. The scoring system used was as follows: 0 — asleep or still; 1 — active; 2 — predominantly active but with bursts of stereotyped sniffing and rearing; 3 — constant stereotyped activity such as sniffing, rearing, or head bobbing, but with locomotor activity still present; 4 — constant stereotyped activity maintained at one location; 5 — constant stereotyped activity but with bursts of licking and/or gnawing and biting; 6 — continual licking of cage grids; and 7 — continual biting of cage grids (Troncone et al., 1988; Tieppo et al., 1997). In addition, the stereotyped behavior was also evaluated by Fray's method (Fray et al., 1980). This method consists of observing the presence or absence of the following behaviors: locomotion, rearing, sniffing, licking and gnawing. The data were recorded simultaneously with the previously described scores.

2.4. Statistical analysis

The results were analyzed by Kruskal–Wallis analysis of variance followed by Mann–Whitney *U*-tests for scores and Fischer's test for Fray's method data. A probability of $P < 0.05$ was taken to reflect significant differences for all comparisons made.

3. Results

3.1. Experiment 1

Pretreatment with SR 27897B and L-365,260 increased apomorphine-induced stereotypy when compared to con-

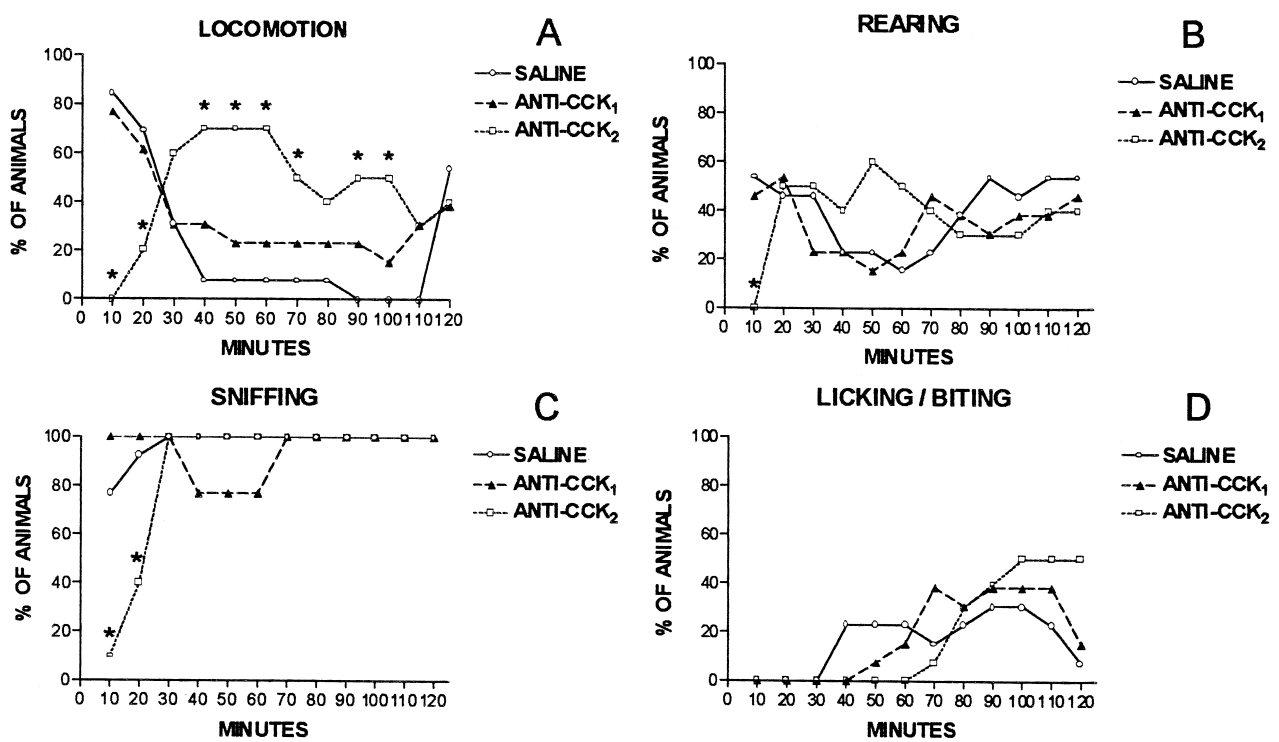

Fig. 4. Time course of Fray's method analysis of amphetamine-induced behavior (9,0 mg/kg). Groups are rats treated i.p. with saline (○–○, $n = 13$), SR 27897B (▲–▲, $n = 13$) or L-365,260 (□–□, $n = 10$) 15 min prior to the behavioral test. Data are percentage of animals that showed the respective behavior. $^{*}P < 0.05$ vs. saline (for *P* values, see Results).

trol (saline). This effect was significant at 30 min for both drugs ($P = 0.030$ saline vs. SR 27897B and $P = 0.044$ saline vs. L-365,260; Fig. 1).

3.2. Experiment 2

In amphetamine-induced stereotyped behavior, pretreatment with SR 27897B was ineffective. L-365,260 decreased significantly the amphetamine-induced stereotypy behavior and this effect was significant at 10 ($P = 0.004$), 40 ($P = 0.005$), 50 ($P = 0.018$), 60 ($P = 0.008$) and 70 ($P = 0.018$) min in the time–response curve (Fig. 2).

Total scores for apomorphine and amphetamine were different (not showed). As we can see in time–response curves (Figs. 1 and 2), the kinetics of these drugs were quite different. Albeit both of them reached the same maximum effect at the same time (30 min), the response to apomorphine decreased abruptly thereafter, while the response to amphetamine was sustained at the same magnitude for 80 min more.

When Fray's method was used to analyze apomorphine data, we observed very low locomotion (a non-stereotyped behavior) in the three groups (Fig. 3A), no differences in rearing (Fig. 3B), a slower decrease in sniffing with both receptors antagonists (significant at 50 min, $P = 0.046$, Fig. 3C) and a drastic increase in licking/biting (an stereotyped behavior) with both receptors antagonists (significant at 30 min, $P = 0.023$, Fig. 3D). Concerning amphetamine, the opposite was observed only with the CCK_2 receptor antagonist, i.e., after a transitory decrease (significant at 10, $P < 0.0001$, and 20 min, $P = 0.036$), a long-lasting increase in locomotion (significant at 40, 50 and 60 min, $P = 0.006$, 90 and 100 min, $P = 0.008$; Fig. 4A), a delay in rearing (significant at 10 min, $P = 0.008$, Fig. 4B) and sniffing (significant at 10, $P = 0.003$, and 20 min, $P = 0.019$, Fig. 4C) and no differences in licking/biting (Fig. 4D) were observed.

4. Discussion

There is a close relation between CCK and dopamine in the striatum. In the dorsal striatum, dopamine increases the veratridine-induced CCK release in vitro (Meyer and Krauss, 1983). Dopamine depletion caused a significant inhibition of K^+-evoked release of CCK (Sierralta and Gysling, 1990). It is also known that the dopaminergic nigrostriatal pathway directly or indirectly regulates the expression of CCK messenger RNA (Schiffmann and Vanderhaeghen, 1992). On the other hand, Vickroy et al. (1988) and Kihara et al. (1993) described a CCK-induced enhancement of dopamine release in the nucleus accumbens but not in the caudate–putamen. This CCK effect may be mediated by either CCK_1 (Vickroy et al., 1988) or CCK_2 receptors (Ghosh and Grasing, 1997; Ladurelle et al., 1997). When intraneostriatal CCK perfusions were used, only the higher dose (100 μM) was effective in increasing dopamine release (Tanganelli et al., 1990). Conversely, microdialysis studies carried out on the caudate–putamen showed that ceruletide, a CCK-like peptide, produces an inhibitory effect on dopamine release (Kihara et al., 1992) and attenuates the haloperidol-induced increase of this release (Kihara et al., 1990).

Other systems may be involved in the effects of CCK on dopamine neurotransmission. It seems that the presence of nitric oxide is necessary to induce hypolocomotion with cerulein, a CCK analogue (Volke et al., 1996). Furthermore, it has been suggested that CCK potentiates the glutamatergic excitatory input to striatum activity via the CCK_2 receptor (Broberger et al., 1998). CCK-8 may also increase dynorphin B and aspartate release in the neostriatum and substantia nigra of the rat. This effect was differently modulated by CCK receptor antagonists depending on the nucleus investigated. The receptors involved in the substantia nigra are CCK_1 and CCK_2, while only CCK_1 is involved and in the neostriatum (You et al., 1996). Dynorphin B in turn decreases dopamine release. This may be one of the reasons why some authors suggest a neuroleptic-like effect of CCK.

CCK reduces dopamine release in the rostral regions and increases extracellular dopamine and its metabolites in the caudal regions of the nucleus accumbens of awake freely moving rats (Ladurelle et al., 1993; Kariya et al., 1994). It has also been suggested that in these regions CCK may both abolish the influence of dopamine from the anterior region on the transmission of motor information and favor that of dopamine from the posterior region on emotional-like responses (Ladurelle et al., 1994). This interrelation is very important for the physiological organization of the brain structures and for the behavioral expressions in which these structures are involved. The present study shows that the specific receptor antagonists for CCK_1 and CCK_2 can differently modulate the stereotypy induced by apomorphine or amphetamine. This fact raises the possibility that endogenous CCK is involved in the organization of stereotyped behavior and further demonstrates the importance of the dopamine–CCK interaction in this behavior. Various CCK receptor antagonists administered alone had no effects on spontaneous locomotor activity (Blacker et al., 1997), exploratory behavior in the plus-maze (Männisto et al., 1994), exploratory locomotion (Crawley, 1992) or conditioned rewards (Josselyn and Vaccarino, 1995). Neither lorglumide, a CCK_1 receptor antagonist, nor L-365,260 administered peripherally at doses 20 times greater than the doses used in the present study induced stereotyped behavior or influenced locomotor activity (Miranda-Paiva and Felicio, 1999).

The difference in the effects of CCK receptor antagonists on amphetamine- and apomorphine-induced stereotypy may be related to differences in the mechanism of action of these two dopaminergic drugs. Namely, amphetamine acts by releasing dopamine while apomorphine

stimulates dopamine receptors. It is reasonable to assume that the differences in the effects of CCK receptor antagonists on these two different drug-induced stereotypes are due to differences in the pharmacodynamic profiles of apomorphine and amphetamine. The stereotyped behaviors elicited by apomorphine and amphetamine agree with those described by Fray et al. (1980).

The present data show that blockade of both CCK_1 and CCK_2 receptors increases apomorphine-induced stereotypy. We have reported previously that intracerebroventricular injections of CCK-8 reduce the expression of apomorphine-induced stereotypy, while CCK-4 does not show such an effect (Tieppo et al., 1997). CCK-8 has almost the same affinity for both receptor subtypes, while CCK-4 shows very low affinity for the CCK_1 receptor, 1000 times lower than CCK-8, and the same affinity as CCK-8 for the CCK_2 receptor (Crawley, 1991). The increase of apomorphine-induced stereotypy observed in SR 27897B-treated animals is consistent with these previous results. The absence of an effect of CCK-4 on apomorphine-induced stereotypy suggests a lack of influence of CCK_2 receptors on this behavior and since CCK_2 blockade stimulated this behavior, the data are apparently contradictory. However, taken together, these results may suggest that CCK might have to bind simultaneously both CCK_1 and CCK_2 receptors in order to fully express its inhibitory effects on apomorphine-induced stereotyped behavior. Since this behavior is a consequence of a direct stimulation of dopamine post-synaptic receptors, this CCK effect may be mainly post-synaptic. Our results agree with previous ones that showed an antistereotypic effect for CCK (Cohen et al., 1982; Zetler, 1986; Tieppo et al., 1995, 1997). On the other hand, Blumstein et al. (1987) described an opposite effect of CCK on stereotyped behavior. Worms et al. (1986) also described a dopaminomimetic effect of intrastriatally injected CCK. This discrepancy may be due to the fact that both of the cited studies used intranuclear injections.

Amphetamine induces stereotypy by releasing dopamine. The present results show that CCK_1 receptor blockade has no effect while a CCK_2 receptor antagonist decreases the expression of amphetamine-induced stereotyped behavior. Amphetamine releases dopamine and CCK (Hurd et al., 1992) and CCK can release dopamine (Vickroy et al., 1988; Tanganelli et al., 1990; Ladurelle et al., 1993, 1997; Kariya et al., 1994; Ghosh and Grasing, 1997). Since CCK potentiates release of dopamine through CCK_2 receptors (Ghosh and Grasing, 1997; Ladurelle et al., 1997), L-365,260 may influence the action of amphetamine by decreasing the release of this catecholamine. These facts suggest that the pre-synaptic action of CCK is possibly mediated by CCK_2 receptors. The effect of the CCK_2 receptor antagonist on amphetamine-induced stereotypy observed in the present study agrees with this hypothesis. The absence of SR 27897B effects on amphetamine-induced stereotypy suggests that the blockade of CCK_1 receptors does not influence mechanisms of stereotypy induction by amphetamine. There is agreement between these data and those reported by Mueller and Whiteside (1990) and Weiss et al. (1988). On the other hand, Kihara et al. (1993) did not find any effect of ceruletide, a CCK analogue, on amphetamine-induced stereotypy.

In conclusion, our results suggest a dual opposite mechanism for CCK–dopamine interactions depending on the pre- or post-synaptic effects of CCK. In addition, our data indicate that both CCK_1 and CCK_2 receptor subtypes play a role in apomorphine-induced stereotypy, while only CCK_2 receptors seem to influence amphetamine-induced stereotyped behavior. They also suggest that both methods, i.e., the observation of apomorphine- and amphetamine-induced stereotypy, should be used whenever the effects of drugs acting on dopamine systems are being assessed.

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