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BRIEF COMMUNICATION

Neurotensin Selectively Antagonizes Apomorphine-Induced Stereotyped Climbing[1]

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JOLICOEUR, F B , M A GAGNE, R. RIVEST, A DRUMHELLER AND S ST-PIERRE *Neurotensin selectively antagonizes apomorphine-induced stereotyped climbing* PHARMACOL BIOCHEM BEHAV **38**(2) 463–465, 1991 —In order to better characterize the neuroleptic properties of neurotensin, the dose-related effects of the peptide on stereotyped climbing, sniffing and licking induced by 0 6 mg/kg apomorphine were examined The following doses of the peptide were injected intraventricularly 30 min prior to apomorphine administration 0 9, 3 75, 30 0 and 60 μg Results indicate that, whereas oro-facial stereotypies remained unaffected by the peptide, stereotyped climbing was significantly decreased with the two largest doses of neurotensin These findings indicate that the profile of neurotensin's neurobehavioral effects is more akin to that of atypical than typical neuroleptics

Neurotensin Apomorphine Stereotypy Climbing Sniffing Licking

SIMILARITIES between the neurobehavioral effects of the tridecapeptide neurotensin and classic neuroleptics were remarked upon early in the literature on the peptide (10). At the time, comparisons were made with typical neuroleptics (phenothiazines and butyrophenones) and, similarly to these substances, neurotensin was found to decrease body temperature, muscle tone and motor activity of animals. Later studies added support to this parallelism by demonstrating that the peptide also decreased rates of self-stimulation in animals and reduced the behavioral hyperactivity induced by a variety of dopamine-stimulating drugs (2, 5, 8). However, as the research on neurotensin progressed, important differences between the actions of the peptide and classic neuroleptics emerged. For example, contrary to typical neuroleptics, neurotensin did not induce catalepsy in rats (4) nor affect oral stereotypies produced by dopaminergic stimulation (2,5). Because of these differences, it has been proposed that neurotensin's profile of neurobehavioral effects is more akin to that of so-called atypical neuroleptics such as sulpiride and clozapine (7). These drugs, while capable of producing all the aforementioned effects of typical neuroleptics, also display weak cataleptogenic properties and are relatively ineffective in affecting stereotyped behaviors

Recently, the examination of the effects of drugs on individual components of apomorphine-induced stereotyped behaviors has been shown to be a valid procedure to detect potential neuroleptics and to differentiate reliably between typical and atypical antipsychotics (3,9). Whereas typical neuroleptics decrease both stereotyped climbing and oro-facial stereotypies at similar doses, atypical neuroleptics are markedly more potent in reducing the former than the latter stereotyped behaviors (3,9). In order to better characterize the neuroleptic-like properties of neurotensin, we have examined in the present study the dose-related effects of the peptide on climbing, sniffing and licking induced by 0 6 mg/kg apomorphine.

METHOD

Animals

Male hooded rats (250–300 g) were obtained from Canadian Breeding Farm (St-Constant, Quebec). They were housed in a temperature-controlled room having a 12-h light/dark cycle. Food (Purina rat chow) and water were available ad lib. Under pentobarbital anesthesia, animals were implanted with a 23-ga stainless steel indwelling guide cannula 2 mm above the left lateral ventricle according to our previously published procedure (6). Animals were allowed at least four days of recovery before the beginning of experimentation

Procedure

Neurotensin was dissolved in 0 9% NaCl and the volume of injection was 10 μl administered over a 30-s period by means of a 50 μl Hamilton syringe. Apomorphine hydrochloride was obtained from Research Biochemicals Incorporated, dissolved in an

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TABLE 1

EFFECTS OF NEUROTENSIN ON APOMORPHINE-INDUCED SNIFFING AND ORAL STEREOTYPIES*

Dose (μg)	Sniffing	Licking
0 0	23 7 ± 2 6	12 7 ± 9 9
0 9	24.9 ± 4 2	19 0 ± 10 9
3 75	24 7 ± 1 7	17 9 ± 9 1
30 0	25 6 ± 1 3	16 5 ± 10 2
60 0	27 9 ± 2 6	17 8 ± 3 0

*Each value represents the mean and standard deviation obtained in each group (n = 7) during the 1-h test period No significant differences between controls and neurotensin-treated animals were found

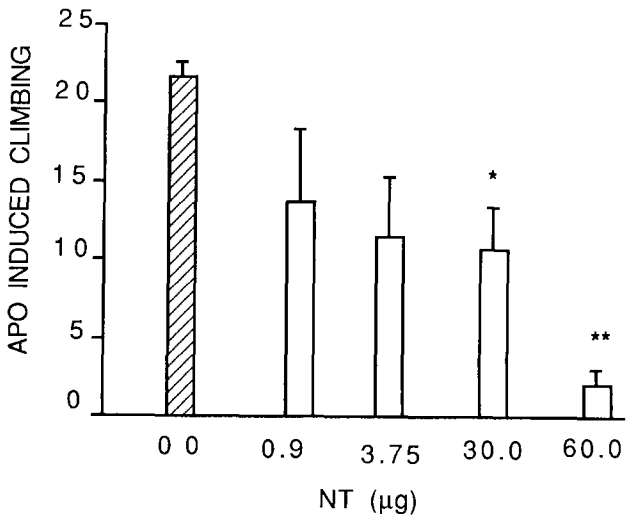

FIG. 1 Dose-related effects of neurotensin on climbing induced by 0 6 mg/kg apomorphine Statistically significant differences from controls as revealed by Dunnett tests are indicated by *$p<0$ 05, **$p<0$ 01

oxygen free boiled 0.9% NaCl solution containing 0.1% ascorbic acid, and administered in a volume of 1 ml/kg.

Data obtained for each behavior were analyzed by individual ANOVA's Each dose administered constituted one level of the main factor. Following a significant main effect, individual group comparisons between controls and neurotensin-treated animals were performed by means of Dunnett tests.

RESULTS

As expected, the administration of 0.6 mg/kg apomorphine induced stereotyped climbing, sniffing and licking in animals Data analysis revealed that none of the doses of neurotensin administered significantly affected the number of either sniffing or licking episodes. These results are presented in Table 1 where mean and standard deviations of both sniffing and licking frequencies obtained in each group are given

On the other hand, climbing behavior decreased linearly as a function of dose and statistically significant reductions were obtained with 30.0 and 60.0 μg of neurotensin. These results are illustrated in Fig. 1 where climbing frequency is presented as a function of dose of neurotensin administered.

DISCUSSION

The results of the present study clearly demonstrate that neurotensin can antagonize apomorphine-induced climbing This effect cannot be attributed to a nonspecific motor impairment effect of the peptide since we have shown previously that 60.0 μg of neurotensin, the most effective dose in reducing climbing, does not affect motor activity nor muscle tone of animals (4). Also, careful observation of the animals during the course of this study did not reveal any behavioral abnormalities. Finally, the maintenance of oral stereotypies in the experimental animals is further indication that inhibition of climbing is not due to a generalized sedative effect of the peptide.

The present results demonstrate for the first time that neurotensin can affect stereotyped behavior induced by a dopamine agonist. Until now examination of the possible influence of the peptide on stereotypy induced by dopaminergic stimulation has been limited to oro-facial stereotypies and a complete lack of effect of the peptide on these behaviors has been reported (2,5). This was confirmed in the present study as both sniffing and licking remained unaffected by neurotensin. The selective inhibitory effect of the peptide on stereotyped climbing is therefore interesting, although the exact mechanism underlying this action is difficult to explain at the present time. The neuronal substrates of apomorphine-induced climbing in rats are essentially unknown but they do not seem to be located in either the striatum or the nucleus accumbens as lesions of these regions do not alter climbing (11). The dopamine receptors implicated in this behavior also remain to be clearly identified (3,9). However, the fact that neurotensin affected climbing but not oro-facial movements indicates that distinct receptors and/or neurophysiological processes underlie these different apomorphine-induced stereotyped behaviors.

Together the present findings lend support to the suggestion that neurotensin's profile of neurobehavioral effects is more akin to atypical than typical neuroleptics. Similarly to atypical antipsychotics neurotensin was much more efficient in reducing climbing than oro-facial stereotypies. Actually, the dissociation of the inhibitory effects on the two types of stereotyped behaviors is even more evident with neurotensin than it is with atypical neuroleptics such as sulpiride and clozapine, which can, at relatively large doses, attenuate oro-facial stereotypies (3,9). Neurotensin, on the other hand, failed completely to attenuate oro-facial stereotypies at the doses utilized in this study. Furthermore, we have observed that a 120.0 μg dose of the peptide, the largest subtoxic dose we could utilize, is also ineffective in altering oro-facial stereotypies (unpublished observations).

In summary, the results of this study demonstrate that neurotensin can selectively affect specific stereotypic manifestations produced by a dopamine agonist. The differential effects of the peptide on stereotyped climbing and oro-facial movements indicate that the peptide possesses atypical neuroleptic-like properties.

REFERENCES

1 Davis, A S , Jenner, P , Marsden, C D A comparison of motor behaviours in groups of rats distinguished by their climbing response to apomorphine Br J Pharmacol 87 129–137, 1986

2 Ervin, G M , Birkemo, L S , Nemeroff, C B , Prange, A J , Jr Neurotensin blocks certain amphetamine-induced behaviors Nature 291 73–76, 1981

3 Gerhardt, S , Gerber, R , Liebman, J M SCH 23390 dissociated from conventional neuroleptics in apomorphine climbing and primate acute dyskinesia models Life Sci 37 2355–2363, 1985

4 Jolicoeur, F B , Barbeau, A , Rioux, F , Quirion, R , St-Pierre, S

Differential neurobehavioral effects of neurotensin and structural analogs Peptides 2 171–175, 1981

5 Jolicoeur, F B , DeMichele, G , Barbeau, A , St-Pierre, S Neurotensin affects hyperactivity but not stereotypy induced by pre- and post-synaptic dopaminergic stimulation Neurosci. Biobehav Rev 7 385–390, 1983

6 Jolicoeur, F B , Rivest, R , St-Pierre, S , Gagne, M A , Dumais, M The effects of neurotensin and [D-Tyr[11]]-NT on the hyperactivity induced by intra-accumbens administration of a potent dopamine receptor agonist Neuropeptides 6 143–156, 1985

7 Jolicoeur, F B , Rioux, F , St-Pierre, S Neurotensin In Lajtha, A , ed Handbook of neurochemistry, vol 8 New York Plenum Press, 1985 93–114

8 Luttinger, D , Nemeroff, C B , King, R A , Ervin, G N , Prange, A J , Jr The effect of injection of neurotensin into the nucleus accumbens on behaviors mediated by the mesolimbic dopamine system in the rat In Chronister, R B V , De France, J F , eds Neurobiology of the nucleus accumbens Sebasco Estates, ME Haer Institute for Electrophysiological Research, 1981 322–332

9 Martres, M P , Sokoloff, P , Delandre, M , Schwartz, J -C , Protais, P , Costentin, J Selection of dopamine antagonists discriminating various behavioral responses and radioligand binding sites Naunyn Schmiedebergs Arch Pharmacol. 325 102–115, 1984

10 Nemeroff, C B Neurotensin perchance an endogenous neuroleptic Biol Psychiatry 15 283–302, 1980

11 Protais, P , Bonnet, J J , Costentin, J , Schwartz, J C Rat climbing behavior elicited by stimulation of cerebral dopamine receptors Naunyn Schmiedebergs Arch Pharmacol 325 93–101, 1984

12 St-Pierre, S , Lalonde, J M , Gendreau, M , Quirion, R , Regoli, D , Rioux, F Synthesis of peptides by the solid phase method Neurotensin, fragments and analogs J Med Chem 24 370–376, 1981

13 Worms, P , Broekkamp, C L E , Lloyd, K G Behavioral effects of neuroleptics In Roth, R H , ed Neuroleptics New York Raven Press, 1983 93–118