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Mediation by neurotensin-receptors of effects of neurotensin on self-stimulation of the medial prefrontal cortex

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1 Intracortical microinjections of neurotensin (NT) selectively decreased intracranial self-stimulation (ICSS) of the medial prefrontal cortex in the rat.

2 To elucidate whether this effect is mediated by NT receptors or by the formation of NT-dopamine complexes, we investigated the effects on ICSS of intracortical microinjections of neurotensin (1-11), an NT fragment that forms extracellular complexes with dopamine but does not bind to NT receptors.

3 We also studied the effects of the peripheral administration of SR 48692, a selective antagonist of NT receptors, on the inhibition of ICSS produced by the intracortical administration of NT.

4 Unilateral microinjections of neurotensin (1-11) at doses of 10, 20 and 40 nmol into the medial prefrontal cortex did not change the basal ICSS rate of this area.

5 The intraperitoneal administration of SR 48692 at doses of 0.08 and 0.16 mg kg^{-1} 30 min before microinjection of 10 nmol of NT into the medial prefrontal cortex, antagonized the inhibition of ICSS produced by the neuropeptide.

6 These results demonstrate that the inhibitory effect of NT on ICSS is mediated by NT receptors.

Keywords: Neurotensin; neurotensin (1-11); SR 48692; medial prefrontal cortex; self-stimulation

Introduction

It has been reported that neurotensin (NT) binds dopamine with high affinity, and generates extracellular NT-dopamine complexes that decrease the availability of dopamine for binding to its specific receptors (Adachi *et al.*, 1990; Schenk *et al.*, 1991). Centrally administered NT exerts a neuroleptic-like action and antagonizes dopamine-dependent locomotor activation (Nemeroff *et al.*, 1983a; Jolicoeur *et al.*, 1985). It has been suggested that the formation of NT-dopamine complexes mediates these behavioural effects (Adachi *et al.*, 1990). In a previous study (Ferrer *et al.*, 1993) we showed that, like dopamine antagonists (Ferrer *et al.*, 1983; Sabater *et al.*, 1993), the intracortical administration of NT selectively decreased intracranial self-stimulation (ICSS) of the rat medial prefrontal cortex. In this cortical area, NT and dopamine are colocalized and simultaneously released by the same terminals in the rat (Studler *et al.*, 1988; Bean *et al.*, 1989; Bean & Roth, 1991). Thus, NT may inhibit ICSS of the medial prefrontal cortex because of the ability of this neuropeptide to bind dopamine. However, this seems unlikely since neuromedin N, an NT analogue that does not bind to dopamine (Adachi *et al.*, 1990) but competes with NT for the same receptor (Minamino *et al.*, 1984; Checler *et al.*, 1986), produces similar inhibitor effects on ICSS of the medial prefrontal cortex (Ferrer *et al.*, 1992).

Electrophysiological studies have shown that most of the neurones in the prefrontal cortex are activated by NT, and that this effect is direct and mediated by NT receptors (Audinat *et al.*, 1989; Stowe & Nemeroff, 1991). Therefore, the inhibitory effect of NT on ICSS of the medial prefrontal cortex may be mediated by NT receptors rather than by complex formation phenomena.

To test this hypothesis, we studied the effects on ICSS in the medial prefrontal cortex of intracortical microinjections of neurotensin (1-11), an NT fragment that, unlike neuromedin N, forms a complex with dopamine but does not bind to the NT receptor (Adachi *et al.*, 1990). We also investigated the effects of the peripheral administration of SR 48692, a recently described selective antagonist of NT receptors (Gully *et al.*, 1993), on the inhibition of ICSS produced by the intracortical administration of NT.

Neurochemical, behavioural and clinical studies have provided evidence for a role of NT in the pathophysiology of schizophrenia and in the mechanism of antipsychotic drug action (see Kasckow & Nemeroff, 1991; Nemeroff *et al.*, 1992 for review). The behavioural effects of NT and its mechanism of action in this area of the cortex are of special interest because alterations in the prefrontal cortex (Weinberger, 1988), including increased concentration of NT, have been reported in schizophrenic patients (Nemeroff *et al.*, 1983b).

Methods

Subjects

Male Wistar rats weighing 250-300 g at the time of surgery were used. The animals were housed individually, provided with food (diet A04, Panlab) and water *ad libitum*, and maintained on a 12-h light (08 h 00 min-20 h 00 min)/12-h dark cycle. All experiments were carried out in accordance with EEC regulations for biological experimentation on animals.

Surgery, training procedure and behavioural testing

Under equithesin anesthesia (2 ml kg^{-1}, i.p.), two monopolar stimulating electrodes and 23-gauge guide cannulae were implanted bilaterally in the medial prefrontal cortex. The tip of each cannula was positioned 0.5 mm rostral and 2.5 mm dorsal to the tip of the ipsilateral electrode. Using the level skull position, stereotaxic coordinates from bregma were: A = +3.7 mm, L = ±0.8 mm and 2.8 mm beneath the dura (Paxinos & Watson, 1986). The implant was fixed to the skull with jeweller's screws and acrylic cement and the cannulae sealed with 30-gauge stilettes. One week after surgery, animals were trained to lever press for 0.3 s trains of 0.5 ms mono-

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phasic, cathodal pulses delivered at a rate of 100 Hz. The intensity of stimulation was adjusted individually after derivation of a rate-intensity curve, and ranged between 100 and 400 μA. The experiments began 1 week after the baseline for ICSS had stabilized. Intracortical microinjections of the peptides were delivered using a 10-μl Hamilton microsyringe mounted on a Harvard infusion pump connected by polyethylene tubing (PE-10) to a 31-gauge injector that protruded 1.5 mm beyond the tip of the guide cannula. The peptides were injected in a total volume of 1 μl over a period of 60 s. The injector was kept in place for an additional 120 s in order to allow diffusion, then withdrawn and replaced by the stilette. The drug solutions were prepared fresh before each experiment. At least 4 days separated each drug test session.

Experimental procedure

In the first experiment we investigated the effects of 10, 20 and 40 nmol of neurotensin (1–11) injected into the right medial prefrontal cortex on ICSS of the ipsilateral side. Since the maximal effect of NT and related peptides on prefrontal ICSS is found almost immediately after administration (Ferrer *et al.*, 1992; 1993), we measured ICSS of the injected medial prefrontal cortex for 5 min before, and during 10 min (divided into two 5-min periods) after, intracortical administration of neurotensin (1–11). Saline microinjections were used as a control for possible nonspecific effects of the vehicle or mechanical manipulation of the injection site.

The second experiment was a time-course study to investigate the effects of i.p. administration of the vehicle (DMSO) and the NT receptor antagonist SR 48692 at doses of 0.04, 0.08, 0.16, 0.64, 1 and 2 mg kg^{-1}, on ICSS of the medial prefrontal cortex. We measured ICSS for 5 min before the i.p. administration of SR 48692 or DMSO (control pre-injection), and during 5-min intervals starting at 15, 30, 60 and 120 min after administration of the drug.

In the third experiment we tested the effects on ICSS of unilateral microinjections of NT alone (10 nmol) and 30 min after the i.p. administration of SR 48692 (0.08 and 0.16 mg kg^{-1}). We measured ICSS in the injected prefrontal cortex for 5 min after the intracortical administration of NT. Intracortical microinjections of saline were used as a control.

Peptides and drugs

Synthetic NT and neurotensin (1–11) were purchased from Sigma (St Louis, MO, U.S.A.). The peptides were dissolved in sterile isotonic saline. SR 48692, {2-[1-(7-chloro-4-quinolinyl)-5-(2,6-dimethoxyphenyl)pyrazol-3-yl)carbonylamino]tricyclo-(3.3.1.1.^{3,7})decan-2-carboxylic acid}. was kindly provided by Dr Gully (Sanofi Recherche, Montpellier, France) and solubilized in dimethyl sulphoxide (DMSO).

Histology and statistical analysis

At the end of the experiments the rats were given an overdose of equithesin and perfused intracardially with saline followed by 10% formalin. The brain was removed and then frozen, sectioned at 40 μm and stained with cresyl-violet. The location of the electrodes and cannulae was checked. The results were analysed statistically by two-way analysis of variance for repeated measures (ANOVA) followed by a Newman-Keuls test or Friedmann analysis of variance when appropriate.

Results

The effect of unilateral intracortical administration of neurotensin (1–11) on ICSS of the injected medial prefrontal cortex is shown in Figure 1. Neurotensin (1–11) at doses of 10, 20 and 40 nmol, as well as the vehicle, produced no significant effects on basal ICSS at 5 and 10 min post-injection, [$F(11,44)=0.31$, $P>0.1$]. Figure 2 shows the effect of the NT receptor antagonist, SR 48692, administered i.p. and the vehicle, on ICSS of the medial prefrontal cortex. To compare the effects on ICSS of the vehicle and the different doses of SR 48692 on the same scale, data are expressed as percentages of their respective pre-injection control. SR 48692 at the doses tested (0.04, 0.08, 0.16, 0.64, 1 and 2 mg kg^{-}) produced no significant changes on ICSS with respect to the injection of vehicle. However, when compared with its respective pre-injection level, SR 48692 at a dose of 0.16 mg kg^{-1} decreased ICSS in the 30 min test period ($P<0.05$).

Figure 3 shows the effects of intracortical administration of NT, before and after blockade of the NT receptors with the selective antagonist, SR 48692, on ICSS of the ipsilateral medial prefrontal cortex. The microinjection of NT (10 nmol) significantly decreased prefrontal ICSS in comparison with the vehicle ($P<0.01$). On the other hand, pretreatment with

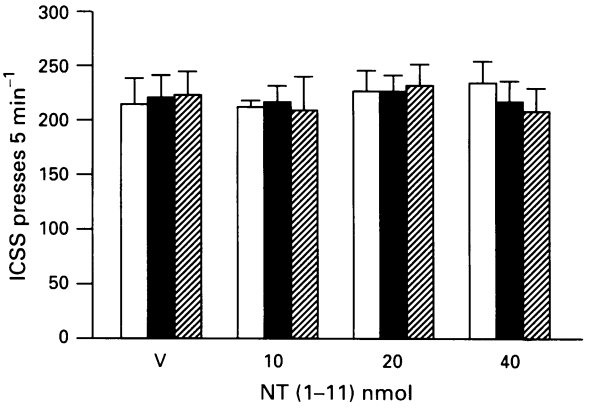

Figure 1 Effects of unilateral microinjections into the medial prefrontal cortex of vehicle (V) and neurotensin (1–11) at doses of 10, 20 and 40 nmol on intracranial self-stimulation (ICSS) of the ipsilateral medial prefrontal cortex. ICSS is expressed as the number of lever presses measured during 5 min prior to microinjection (open columns) and during two consecutive periods of 5 min postinjection (solid and hatched columns respectively). Values are the mean ± s.e.mean from 5 rats.

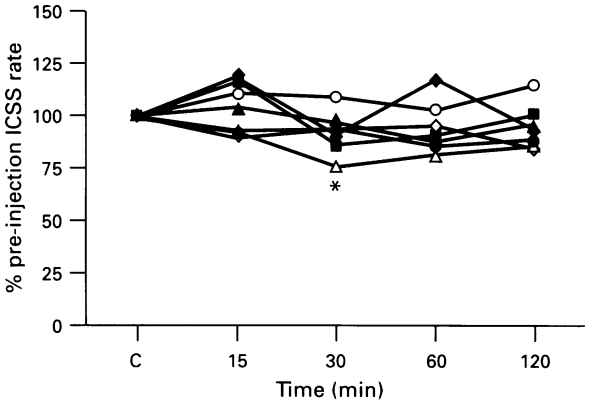

Figure 2 Effects of intraperitoneal administration of different doses of the NT antagonist, SR 48692 and the vehicle on intracranial self-stimulation (ICSS) of the medial prefrontal cortex. ICSS was measured as the number of lever presses during 5 min prior to the i.p. administration of the drug (control pre-injection) and during 5 min intervals at 15, 30, 60 and 120 min postinjection. Data are expressed as the percentage of the respective control pre-injection ICSS rate (C). (■) Vehicle SR 48692; SR 48692 at: (○) 0.04 mg kg^{-1}; (◇) 0.08 mg kg^{-1}; (△) 0.16 mg kg^{-1}; (●) 0.64 mg kg^{-1}; (◆) 1 mg kg^{-1}; (▲) 2 mg kg^{-1}. Values represent the mean of 5 rats. Statistical significance was determined by Friedman two-way analysis of variance. Dose of 0.16 mg kg^{-1} at 30 min intervals *vs* control pre-injection: $*P<0.05$.

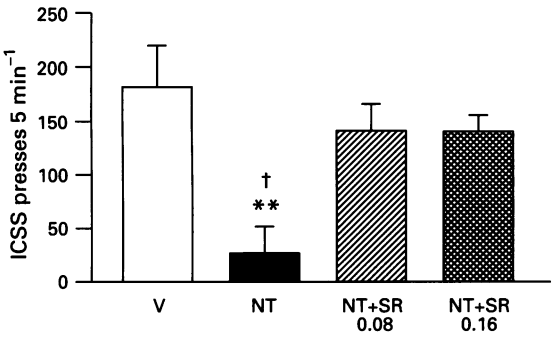

Figure 3 Effects of unilateral intracortical microinjections into the medial prefrontal cortex of saline (open column), 10 nmol of neurotensin (NT) alone (solid column) and 10 nmol of NT 30 min after the i.p. administration of the NT antagonist SR 48692 at doses of 0.08 mg kg^{-1} (hatched column) and 0.16 mg kg^{-1} (cross-hatched column) on intracranial self-stimulation (ICSS) of the ipsilateral side. ICSS is expressed as the number of lever presses measured during 5 min after microinjections. Values represent the mean ± s.e.mean from 4 rats. $^{**}P<0.01$ *vs* saline. $\dagger P<0.05$ *vs* neurotensin + SR 48692 (0.08 and 0.16 mg kg^{-1}).

SR 48692 (0.08 and 0.16 mg kg^{-1}) antagonized the inhibition on ICSS produced by NT. The effect of SR 48692 was significant at both of doses tested ($P<0.05$).

Histological analysis showed that the electrodes were placed in the deep layers of the medial prefrontal cortex, as described in previous studies (Ferrer *et al.*, 1992; 1993). These layers constitute the main terminal field of the NT-dopamine mesocortical fibres (Studler *et al.*, 1988; Tassin *et al.*, 1992).

Discussion

As previously reported (Ferrer *et al.*, 1993), microinjection of NT into the medial prefrontal cortex decreased ICSS of this area. We have suggested that the inhibitory effect of NT is not due to this peptide's ability to bind dopamine (Ferrer *et al.*, 1992; 1993). The lack of effect on prefrontal ICSS of neurotensin (1–11), an NT fragment that binds dopamine with high affinity (Adachi *et al.*, 1990), is consistent with this interpretation.

Neurotensin (1–11) does not bind to the NT receptor because it lacks the C-terminus required to interact with these receptors (Checler *et al.*, 1986; Adachi *et al.*, 1990). Thus, unlike NT and neuromedin N, neurotensin (1–11) failed to produce those behavioural or electrophysiological actions which it has been suggested are mediated by NT receptors (Stowe & Nemeroff, 1991). The fact that neurotensin (1–11) produced no effect on prefrontal ICSS also suggests that the inhibition of ICSS produced by NT may be mediated by NT receptors. The results obtained in the present study with SR 48692, a recently described selective nonpeptide antagonist of NT receptors (Gully *et al.*, 1993), further support the hypothesis that NT receptors participate in the inhibitory action of NT on prefrontal ICSS. Pretreatment with SR 48692, 30 min before microinjection of NT into the medial prefrontal cortex, prevented the inhibition of prefrontal ICSS. Similar evidence of antagonism of NT-mediated behaviour by SR 48692 has been reported by Gully *et al.* (1993). These authors have shown that the previous administration of SR 48692, at times and in doses similar to those used in the present study, reduced the turning behaviour induced by the intrastriatal injection of NT.

In the prefrontal cortex, most NT receptors are distributed on the membrane of intrinsic non-dopaminergic prefrontal neurones (Schotte & Leysen, 1989; Tassin *et al.*, 1992). These cells are the neural substrate that supports ICSS of the medial prefrontal cortex (Ferrer *et al.*, 1985). Electrophysiological studies have shown that NT depolarizes most of the prefrontal cortex neurones, and that this effect is direct and due to the activation of NT postsynaptic receptors on the recorded pyramidal cells (Audinat *et al.*, 1989; Stowe & Nemeroff, 1991). In the light of this evidence, our results strongly suggest that the inhibition of ICSS in the medial prefrontal cortex produced by the local administration of NT is mediated by the activation of NT receptors on prefrontal neurones.

Previous studies have shown that certain NT responses, such as the dopamine releasing effects of NT in guinea-pig striatal slices, or the inhibition of turning behaviour induced by the unilateral intrastriatal injection of NT in the mouse, are mediated by the cloned high-affinity rat brain NT receptor and antagonized by SR 48692 (Gully *et al.*, 1993). However, SR 48692 did not reverse the hypothermic and analgesic effects of NT, which seem to be mediated by a different subtype of NT receptor (Labbé-Jullié *et al.*, 1994; Dubuc *et al.*, 1994). The fact that SR 48692 antagonized the inhibition of ICSS induced by NT suggests that the cloned high-affinity rat brain receptor mediates the effects of NT on ICSS of the rat medial prefrontal cortex.

Several endogenous neurotransmitters, including dopamine, acetylcholine and substance P, are known to participate in ICSS of the prefrontal cortex (Mora & Ferrer, 1986; Ferrer *et al.*, 1988). The effects of manipulation of one of the neurotransmitters involved in this behaviour may thus be masked or compensated by the activity of the other neurotransmitters also released by electrical stimulation of this area, e.g. depletion of dopamine levels in the prefrontal cortex produces only a partial decrease of this behaviour and basal self-stimulation rate is recovered one month after dopamine depletion (Phillips & Fibiger, 1978; Simon *et al.*, 1979). This could explain why the peripheral administration of SR 48692 alone had little or no effect on ICSS. In line with this interpretation, we recently found that the central administration of selective inhibitors of the peptidases that inactivate endogenous NT also had little effect on ICSS of the medial prefrontal cortex (Fernández *et al.*, 1996).

Although the present results rule out the formation of NT-dopamine complexes as a mechanism responsible for the effects of this peptide on ICSS, the participation of other types of NT-dopamine interaction cannot be entirely discarded. Others have shown that NT potentiates K^+-evoked dopamine release in slices of prefrontal cortex (Hetier *et al.*, 1988), and enhances dopamine turnover in this area after central administration (Drumheller *et al.*, 1990). More research is needed to elucidate whether dopamine mediates the effects of NT on ICSS of the prefrontal cortex.

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