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Effects of excitotoxic lesions of the medial prefrontal cortex on density of high affinity [^{125}I-Tyr3]neurotensin binding sites within the ventral midbrain and striatum

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Abstract

The present study was aimed at determining the extent to which excitotoxic lesions of the medial prefrontal cortex reduce neurotensin receptors within the striatum, the nucleus accumbens, the ventral tegmental area and the substantia nigra. The medial prefrontal cortex was unilaterally lesioned with ibotenic acid and 10 days later brain sections were processed for neurotensin receptor autoradiographic analysis using 0.1 nM [^{125}I-Tyr3]neurotensin with, or without, levocabastine. Analysis revealed at least two sites, one levocabastine-insensitive neurotensin NT_1 and one levocabastine-sensitive neurotensin NT_2-like. The proportion of the latter site was high within the caudal striatum, the nucleus accumbens and the medial prefrontal cortex. Lesions produced a 60% to 80% reduction in neurotensin NT_1 within the ipsilateral medial prefrontal cortex, but no change in the sub-cortical nuclei. An increase in neurotensin NT_2-like receptors was found in ipsilateral dorso-caudal caudate. These results show that a significant amount of neurotensin NT_1 receptors are located on neurons within the medial prefrontal cortex but not on their efferent terminals.

Keywords: Dopamine; Excitotoxic lesion; Neurotensin; Prefrontal cortex; Striatum

1. Introduction

Neurotensin is an endogenous neuropeptide that acts as a neurotransmitter and neuromodulator in limbic brain regions that contain dopamine cell bodies and terminals (Binder et al., 2001). The functional interactions between dopamine and neurotensin have conferred to the peptide a role in disorders such as schizophrenia and drug addiction. For instance, intracerebroventricular injections of neurotensin potentiate reward and lead to a lasting increase in the behavioral stimulant effects of amphetamine (Blackburn et al., 2004; Rompré, 1995). When injected into the ventral midbrain, neurotensin also enhances dopamine neurotransmission (Sotty et al., 2000; Steinberg et al., 1995) and stimulates dopamine-dependent behaviors (Kalivas and Duffy, 1990; Rompré et al., 1992). But when injected into the nucleus accumbens, neurotensin blocks the behavioral effects of psychostimulant drugs (Kalivas et al., 1984; Robledo et al., 1993) and, interestingly, its blocks the stimulant effect of neurotensin injected into the ventral midbrain (Kalivas et al., 1982). Such findings led to the hypotheses that neurotensin may act as either an endogenous antipsychotic or an endogenous psychostimulant (Berod and Rostene, 2002; Kinkead and Nemeroff, 2002).

To date, three neurotensin receptors have been characterized in the brain: a first receptor named neurotensin NT_1 displays a high affinity for neurotensin (Tanaka et al., 1990; Vita et al., 1993); a second receptor, neurotensin NT_2, displays a lower affinity for neurotensin and acts as a binding site for levocabastine, a histamine H_1 receptor antagonist (Chalon et al., 1996). Both, neurotensin NT_1 and neurotensin NT_2, are 7-transmembrane spanning G-protein coupled receptors. A third neurotensin receptor (NT_3) was discovered more recently; it is mainly localized within the cytoplasm and is similar to the

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previously characterized gp95/sortilin receptors; to date it is considered not as a functional receptor but a binding site (Mazella et al., 1998).

The high affinity neurotensin NT_1 receptor is found in relatively high densities within dopamine innervated limbic nuclei. In the ventral midbrain, for instance, it is found within the ventral tegmental area and the substantia nigra, mostly on dopamine neurons and, to a lesser extent, on axon terminals (Boudin et al., 1996, 1998). Within the nucleus accumbens and the caudate, neurotensin NT_1 are mostly found on axon terminals which is consistent with lack, or low level, of neurotensin NT_1 mRNA (Alexander and Leeman, 1998; Nicot et al., 1994). The fact that neurotensin NT_1 receptors are found on axon terminals suggests that neurotensin modulates dopamine neurotransmission by acting presynaptically on receptors located on either dopaminergic or non-dopaminergic afferent terminals. One possible source of the non-dopaminergic afferents is the medial prefrontal cortex. In effect, the medial prefrontal cortex send efferents to these regions and a substantial amount of evidence shows that they modulate subcortical dopamine neurotransmission (Sesack and Pickel, 1992; Vertes, 2004). The medial prefrontal cortex also contains neurotensin NT_1 mRNA and neurotensin NT_1 proteins (Alexander and Leeman, 1998; Boudin et al., 1996) some being expressed on pyramidal cells that give rise to medial prefrontal cortex efferents to subcortical regions (Petrie et al., 2005). The present study was aimed at determining the extent to which neurotensin NT_1 receptors are expressed by medial prefrontal cortex perikarya and by terminals of medial prefrontal cortex efferents to the ventral midbrain, the nucleus accumbens and the caudate. Using autoradiography, we measured the density of neurotensin NT_1 receptors within these limbic areas several days after a unilateral excitotoxic lesion of the prelimbic and infralimbic areas of the medial prefrontal cortex.

2. Material and methods

The experiment was carried out in accordance with the Canadian Council on Animal Care Guide to the Care and Use of Experimental Animals. An internal animal care committee approved all experiments and all efforts were made to minimize animal discomfort.

2.1. Surgery and histological analysis

Adult male Long–Evans rats were injected with atropine methylnitrate (0.4 mg /kg, i.p.), anesthetized 20 min later with sodium pentobarbital (65 mg/kg, i.p.) and then placed on a stereotaxic frame. The surface of the cranium was exposed and the bone and dura above the right prefrontal cortex were removed. A 1-μl solution containing 2 μg of ibotenic acid (Research Biochemicals International, Natick, MA, USA), or the vehicle alone, was unilaterally injected at three different anterior–posterior locations (spaced 0.75 or 0.5 mm apart) between 3.25 and 4.5 mm anterior to the bregma, 0.5 mm lateral to midline and 4.5 mm ventral to the surface of cranium (Paxinos and Watson, 1998). Solutions were injected over a period of 6 min via a microinfusion pump using a glass micropipette with the tip broken down to 35–45 μm; the pipette was moved up by 0.5 mm after injection of 0.5 μl and was left in place for an additional minute at the end of the injection. Ten days later, animals were killed by decapitation, the brain removed, frozen at −30 °C in *N*-methyl-butane, and stored at −80 °C. This procedure has been previously used to reveal the existence dopamine D1 receptors on prefrontal cortex terminals with the ventral midbrain (Dewar et al., 1997). Using a cryostat, transverse sections (20 μm thick) were collected and thaw-mounted onto glass slides. In both sham and lesioned animals, the extent of the excitotoxic lesion and of the unspecific damage was determined by light microscopic examination of formal-thionin stained 20 μm sections.

2.2. Autoradiography

Neurotensin receptors were labeled according to a well-established procedure (Boudin et al., 1998; Kitabgi et al., 1987). Briefly, slide mounted tissue sections were defrosted at 4 °C and preincubated for 30 min in cold (4 °C) 50 mM Tris–HCl buffer, pH 7.4 supplemented with 5 mM $MgCl_2$, 0.2% bovine serum albumin (Sigma Co.) and 5 μM orthophenanthroline (Aldrich). They were then incubated at 4 °C for 60 min in the same buffer with 0.1 nM [^{125}I-Tyr3]neurotensin (2200 Ci/mmol; Perkin Elmer) with or without 1 μM levocabastine. Nonspecific binding was determined in adjacent sections incubated (without levocabastine) with the radioligand in the presence of 1 μM unlabeled neurotensin. Sections were then washed with ice-cold buffer (5 × 2 min) and dried under a stream of cold air. Autoradiograms were generated by opposing the slides against iodinated sensitive film (Kodak Biomax MS Film) together with iodate standards ([^{125}I] microscales, Amersham Biosciences) for 5 days at 4 °C. Quantitative measurements were obtained with a microcomputer-based image analysis system (MCID, Imaging Research). Standard curves were generated from ([^{125}I] microscales and were used to convert density values in fmol/mg of protein. Multiple readings were made for each region (3–5 sections for each brain region per animal). In all of the regions analyzed, radioligand binding was completely abolished in the presence of 1 μM neurotensin, hence showing that at this concentration nonspecific binding was minimal if not absent.

Statistical significance was determined with a 3-way [levocabastine (2 levels), lesion (2 levels), brain side (2 levels) analysis of variance (ANOVA) and comparisons among means were made with Duncan's multiple range post-hoc test, and the level of significance set at 0.05 (Statistica V5.0, Statsoft).

3. Results

3.1. Lesion data

Histological analysis (see Fig. 1 for a histological reconstruction of the lesions) revealed that ibotenic acid

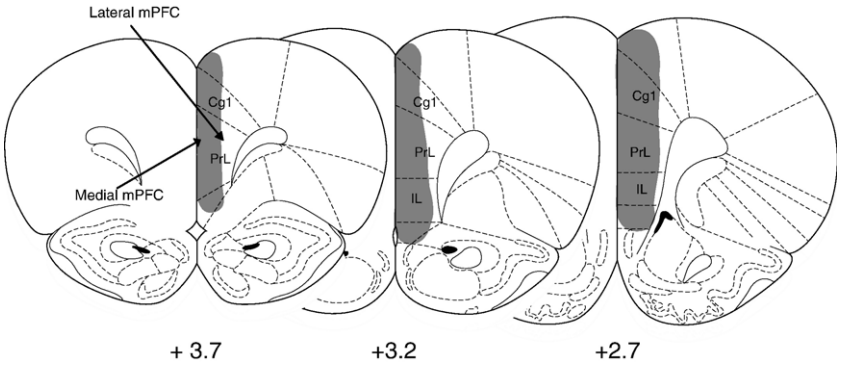

Fig. 1. Reconstruction showing coronal brain sections highlighting areas of the prefrontal cortex (shaded regions) lesioned using ibotenic acid. The number below each section represents the distance in mm relative to bregma according to the strereotaxic atlas of Paxinos and Watson, 1998. Cg1 = cingulate cortex, area 1; PrL = prelimbic cortex; IL = infralimbic cortex.

induced a decrease in cells over a region that extends from the anterior portion of the medial prefrontal cortex to the rostral pole of the cingulate cortex mostly within the prelimbic and the infralimbic cortices; a comparison with sham animals showed that cortical layer organization was completely absent in the lesioned animals. No such apparent damage was found in the cortical tissue contralateral to the injection site. Only animals with a confirmed lesion were selected for autoradiographic analyses.

3.2. Autoradiographic data

In sham animals, a high density of [^{125}I-Tyr3]neurotensin specific binding (without levocabastine treatment and referred to as total specific binding below) was observed in the medial and lateral aspects of the medial prefrontal cortex. In the presence of levocabastine, the total binding was reduced by more than 30% (Fig. 2, top panels) showing that at the concentration used (0.1 nM) the ligand binds to a levocabastine-insensitive (neurotensin NT_1) and a levocabastine-sensitive (presumed to be neurotensin NT_2) receptor. Excitotoxic lesions reduced neurotensin NT_1 receptors by 64% on the ipsilateral side in the lateral prefrontal cortex, and reduced it on the contralateral side to an extent that did not reach statistically significance (Fig. 2 left panel and Fig. 3, top panel). Within the medial aspect of the medial prefrontal cortex, neurotensin NT_1 receptors were significantly reduced on both hemispheres; by 93% on the ipsilateral and by 49% contralateral to the lesion (Fig. 3, bottom panel). The density of neurotensin receptors labeled in the absence of levocabastine (neurotensin NT_1 and neurotensin NT_2) was reduced by near the same percentages.

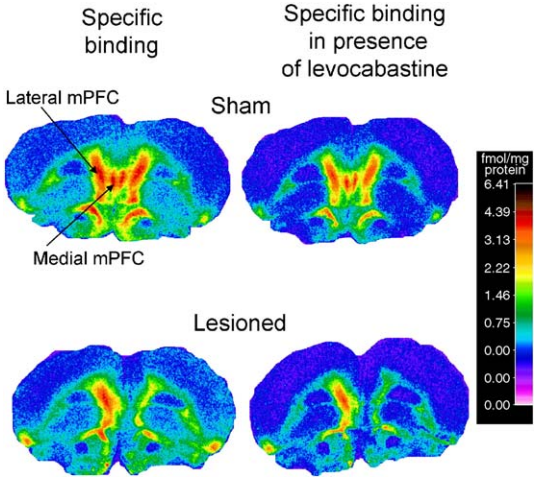

Fig. 2. Computer-generated autoradiograms illustrating [^{125}I-Tyr3]neurotensin binding within the medial prefrontal cortex (mPFC) for one sham (top panels) and one lesioned (bottom panels) animal.

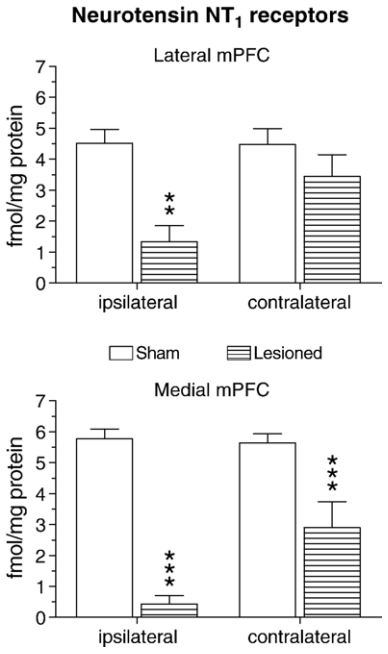

Fig. 3. Density of neurotensin NT_1 receptors (expressed in fmol/mg of proteins) in the lateral (top panel) and medial (bottom panel) part of the medial prefrontal cortex (mPFC) in sham and lesioned animals. Data represent mean ± S.E.M. (n=4, each group). The ANOVA yielded significant of levocabastine (lateral mPFC: $F_{1,12}$=6.1, P<0.05; medial mPFC, $F_{1,12}$=7.3, P<0.05) and lesion effects (lateral mPFC: $F_{1,12}$=18.2, P<0.001; medial mPFC, $F_{1,12}$=39.0, P<0.001). Asterisks indicate a statistically significant difference with sham (**P<0.01; ***P<0.001).

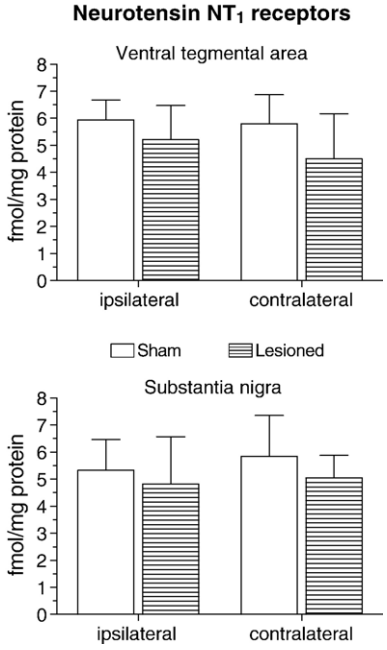

Fig. 4. Density of neurotensin NT_1 receptors (expressed in fmol/mg of proteins) in the ventral tegmental area (top panel) and the substantia nigra (bottom) in sham and lesioned animals. Data represent mean±S.E.M. (n=4 per group). The ANOVA yielded significant no effect of levocabastine (ventral tegmental area: $F_{1,10}$=0.04, P=0.85; substantia nigra, $F_{1,10}$=0.02, P=0.89) and of lesion (ventral tegmental area, $F_{1,10}$=0.51, P=0.49; substantia nigra, $F_{1,10}$=0.08, P=0.77).

A high density of [^{125}I-Tyr3]neurotensin specific binding was also observed in the ventral midbrain of sham animals within the ventral tegmental area and the substantia nigra. Levocabastine failed to reduce the total specific binding suggesting that the ligand selectively labeled neurotensin NT_1 receptors within these nuclei. Lesions of the medial prefrontal cortex also failed to reduce neurotensin NT_1 binding within both nuclei (Fig. 4).

Within the nucleus accumbens of sham animals the density of [^{125}I-Tyr3]neurotensin specific binding was much lower than that measured in the ventral midbrain, but in this nucleus levocabastine led to a reduction (more than 60%) in the total specific binding, an effect that did not reach statistical significance however ($F_{1,12}$=3.92, P=0.07). Neither neurotensin NT_1 receptors nor total specific binding were reduced by medial prefrontal cortex lesions (see Table 1).

Within the striatum (caudate nucleus), the density of [^{125}I-Tyr3]neurotensin specific binding (without levocabastine treatment) was heterogeneous, being higher in rostral and ventro-caudal regions than in the dorso-caudal part (see Table 1). Levocabastine produced a large decrease (more than 80%) in total specific binding in the dorso-caudal ($F_{1,12}$=7.99, P<0.05) and a smaller but statistically significant decrease in ventro-caudal ($F_{1,12}$=6.97, P<0.05) striatum; such a decrease was not observed in the rostral striatum ($F_{1,12}$=1.91, P=0.19). Interestingly, lesions of the medial prefrontal cortex tended to produce an increase in total specific binding in the ipsilateral dorso-caudal striatum but this effect did not reach statistical significance ($F_{1,12}$=4.51, P=0.054).

4. Discussion

The present results demonstrate that at a concentration of 0.1 nM, [^{125}I]neurotensin binds to a levocabastine-sensitive and a levocabastine-insensitive receptor within the medial prefrontal cortex and the caudal part of the striatum, results consistent with a previous study (Kitabgi et al., 1987). The first site most likely corresponds to the neurotensin NT_1 receptor as it is insensitive to levocabastine and displays sub-nanomolar affinity for neurotensin (Tanaka et al., 1990; Vita et al., 1993). Moreover, its presence within these brain structures has been confirmed with immunohistochemistry methods (Boudin et al., 1996). The second binding site may correspond to the cloned neurotensin NT_2 receptor which displays a high affinity for levocabastine (Chalon et al., 1996); it is present within the medial prefrontal cortex and the striatum (Sarret et al., 2003). The rather large contribution of this receptor to the total specific neurotensin binding signal (between 30% (medial prefrontal cortex)) and 80% (dorso-caudal striatum) was rather unexpected because its K_D for neurotensin is 20 to 30 times higher than the concentration used in the present study (Chalon et al., 1996). Moreover, within the substantia nigra and the ventral tegmental area, two regions that contain neurotensin NT_2 receptors (Sarret et al., 2003), levocabastine failed to

Table 1
Effect of ibotenic acid lesion of the medial prefrontal cortex on 0.1 nM [^{125}I]neurotensin specific binding in the absence and in the presence of 1 μM levocabastine within sub-regions of the striatum (data represent mean±S.E.M.)

	Sham (n=4)		Lesioned (n=4)	
	Specific binding (fmol/mg protein)	Specific binding+levocabastine (fmol/mg protein)	Specific binding (fmol/mg protein)	Specific binding+levocabastine (fmol/mg protein)
Rostral	I: 2.58±0.3	I: 2.10±0.25	I: 2.35±0.6	I: 1.44±0.14
	C: 2.40±0.44	C: 1.88±0.35	C: 2.24±0.6	C: 1.75±0.3
Ventro-caudal	I: 1.96±0.13	I: 1.64±0.12	I: 1.99±0.23	I: 1.19±0.33
	C: 1.71±0.25	C: 1.34±0.24	C: 1.53±0.24	C: 0.84±0.24
Dorso-caudal	I: 0.24±0.05	I: 0.03±0.02	I: 0.73±0.18	I: 0.17±0.17
	C: 0.37±0.07	C: 0.07±0.05	C: 0.50±0.21	C: 0.27±0.16
Nucleus accumbens	I: 0.88±0.1	I: 0.37±0.09	I: 0.82±0.19	I: 0.59±0.3
	C: 0.76±0.06	C: 0.26±0.11	C: 0.70±0.22	C: 0.44±0.27

I: ipsilateral.
C: contralateral.

reduce [^{125}I-Tyr3]neurotensin total binding, results also found by Szigethy and Beaudet (1989). Since the neurotensin NT_2 receptor is a G-protein coupled receptor, it could be then that it is expressed in a low and in a high affinity state in different brain regions and under different conditions; the evidence for this is however still lacking. An alternative hypothesis is that this second site corresponds to a new high affinity, levocabastine-sensitive neurotensin receptor being expressed in some limbic brain regions such as the medial prefrontal cortex and the striatum but not in others like the ventral midbrain. The existence of such a neurotensin NT_2-like receptor has been proposed previously on the basis of pharmacological data (Chalon et al., 1996; Nouel et al., 1997; Tyler et al., 1998). These results demonstrate that our procedure allowed us to selectively marked neurotensin NT_1 receptors in the brain regions studied.

The lesions destroyed a large portion of the medial prefrontal cortex, mainly the infralimbic, prelimbic and to a certain extent the ventral part of anterior cingulated cortex. In the sham animals, a high density of neurotensin NT_1 was found in the medial and the lateral medial prefrontal cortex, and in lesioned animals the density of these receptors was greatly reduced. In as much as the excitotoxic lesion was selective this shows that neurotensin NT_1 receptors are mainly located on cell bodies and dendrites of projection neurons and/or interneurons. This finding is consistent with the presence of neurotensin NT_1 mRNA within the medial prefrontal cortex (Alexander and Leeman, 1998; Nicot et al., 1994) and with a previous immunohistochemical study showing that a large amount of neurotensin NT_1 are on pyramidal and non-pyramidal cells within the infralimbic and prelimbic (Petrie et al., 2005). A decrease in neurotensin NT_1 was also observed contralateral to the lesion within the medial prefrontal cortex, an effect that cannot be attributed to spreading of the lesion to this side according to histological analysis. A most likely explanation is that neurotensin NT_1 receptors were lost following destruction by anterograde degeneration of afferent terminals originating from the ipsilateral side. Anatomical studies have shown that medial prefrontal cortex neurons project to the contralateral medial prefrontal cortex, within the medial and lateral regions that contain neurotensin NT_1 receptors (Sesack et al., 1989; Vertes, 2004). This hypothesis is also supported by previous study showing that neurotensin NT_1 are expressed on perikarya and axons/nerve terminals within the frontal cortex (Boudin et al., 1996).

An important aim of this study was to determine whether neurotensin NT_1 receptors are located on medial prefrontal cortex afferent terminals to sub-cortical nuclei, such as the nucleus accumbens, the caudate and the ventral midbrain.

The ventral tegmental area and the substantia nigra receive an important innervation from the medial prefrontal cortex (Sesack et al., 1989; Vertes, 2004) and contain a high density of neurotensin NT_1 receptors (Boudin et al., 1996; Szigethy and Beaudet, 1989). Although the majority of these neurotensin NT_1 are located on perikarya, some of them are found on axons and nerve terminals (Boudin et al., 1998). Since medial prefrontal cortex lesions failed to alter neurotensin NT_1 receptor density, we can conclude that the receptors are not expressed on medial prefrontal cortex afferent axons and terminals to the ventral tegmental area and the substantia nigra.

The nucleus accumbens also receive an important innervation from the medial prefrontal cortex (Sesack et al., 1989; Vertes, 2004) and contain a low density of neurotensin NT_1 receptors that are mainly located on axon terminals (Delle Donne et al., 2004; Pickel et al., 2001); this is consistent with the lack of neurotensin NT_1 mRNA in this region (Alexander and Leeman, 1998). Our results show that the amount of both neurotensin NT_1 and neurotensin NT_2-like receptors in the accumbens is not affected by lesioning of the medial prefrontal cortex, suggesting that they are not expressed on afferents from this cortical region. The rostral and caudal striatum, defined as rostral and caudal to the decussation of the anterior commissure, were examined separately. Our results show that neurotensin NT_1 receptors constitute a minor proportion of the neurotensin receptors within the dorsal part of the caudal striatum whereas they predominate in the ventral part. The analysis shows that medial prefrontal cortex lesion did not alter the density of neurotensin NT_1 receptors within the three striatal regions studied, suggesting that they are mainly located on local neurons and/or other afferent terminals such as dopamine (Cadet et al., 1991; Schotte and Leysen, 1989). This finding is inconsistent though with the 20% reduction in striatal neurotensin receptors following ablation of the frontal cortex reported by Goedert et al. (1984); the type and extent of cortical damage and the lack of control for levocabastine-sensitive binding may likely account for this discrepancy.

Neurotensin is likely to act on neurotensin receptors within the medial prefrontal cortex to modulate sub-cortical dopamine. Microinjections of neurotensin, and of SR-48692, a preferential neurotensin NT_1 antagonist, directly into the medial prefrontal cortex alter dopamine cell firing and subcortical dopamine release, effects likely mediated by neurotensin NT_1 expressed by medial prefrontal cortex neurons (Rompré et al., 1998; Santucci et al., 1997). Repeated ICV injections of neurotensin, and of its potent analog D-Tyr[11] neurotensin, produce a lasting potentiation of the locomotor stimulant effect of amphetamine, and this is prevented by excitotoxic lesions of the medial prefrontal cortex (Blackburn et al., 2004). This latter finding is consistent with the critical role of medial prefrontal cortex efferents in the development of amphetamine sensitization (Cador et al., 1999; Wolf et al., 1995). Our results would suggest that neurotensin and its analog initiate the sensitization to amphetamine by acting on neurotensin NT_1 receptors located within the medial prefrontal cortex and not on medial prefrontal cortex efferents to dopamine innervated subcortical nuclei.

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