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Neuronal Sites Mediating Locomotor Hyperactivity Following Central Neurokinin Agonist Administration

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ELLIOTT, P. J., J. M. PARIS, H. MITSUSHIO AND S. A. LORENS. *Neuronal sites mediating locomotor hyperactivity following central neurokinin agonist administration.* PHARMACOL BIOCHEM BEHAV **37**(2) 329–333, 1990.—The stable substance P analog, DiMeC7, increases spontaneous locomotor activity after infusion into the lateral ventricles or median raphe nucleus (MRN). The elevated locomotion observed after intracerebroventricular (ICV) infusion of DiMeC7 was attenuated, but not blocked, by bilateral 6-hydroxydopamine (6OHDA) lesions of the ventral tegmental area (VTA). In contrast, bilateral 6OHDA lesions of the nucleus accumbens (NAS) blocked the motor activity induced by ICV administration of DiMeC7. Similar lesions did not affect the increases in motor behavior observed after MRN infusions of DiMeC7. However, the hyperactivity following MRN microinjections of DiMeC7 was attenuated by intraperitoneal administration of the dopamine (DA) antagonist, haloperidol. The results suggest that ICV infusions of DiMeC7 increase locomotor activity by acting directly on neurones in the NAS and in part by influencing, directly or indirectly, the activity of DA cells in the VTA. The increased motor activity seen after MRN administration of DiMeC7 appears to depend on DA neurons but not on projections to the NAS.

Substance P DiMeC7 Dopamine 6-Hydroxydopamine GABA Muscimol Ventral tegmental area Nucleus accumbens Intracerebroventricular Median raphe nucleus Locomotor activity

MICROINJECTION of endogenous neurokinins or the stable substance P (SP) analog, [pGlu^5,MePhe^8,Sar^9] substance P_{5-11} (DiMeC7), into the ventral tegmental area (VTA) or the lateral ventricles elevates motor activity (3, 4, 7, 11). This neurokinin-induced behavioral activation appears to depend upon dopaminergic neurons since systemic administration of the dopamine (DA) antagonist haloperidol attenuates the motor response elicited via both routes of administration (7,11). Biochemical studies also support the interaction between the neurokinins and midbrain DA systems (3, 6, 9). Moreover, SP infusions into the nucleus accumbens (NAS) elevate DA metabolites in the same tissue indicating increases in DA release (10), whereas immuno-neutralization of SP in the NAS has the opposite effect (8). Hence, endogenous SP within the NAS would appear to regulate DA release within the NAS and may therefore be critical in the expression of motor activity. Although the intra-VTA microinjections of tachykinins can activate the well-characterized VTA-NAS DA pathway, the mechanism by which intracerebroventricular (ICV) infusion of the neurokinins increases motor activity is unknown (6).

Recently, it has been demonstrated that infusions of DiMeC7 and naturally occurring neurokinins into the median raphe nucleus (MRN) produce dose-dependent increases in motor activity (14–16). This increase is not due to diffusion of agents to the nearby VTA since ibotenic acid lesions of the MRN prevented the locomotor increases observed after intra-MRN DiMeC7 infusions (14). Furthermore, the elevated motor activity elicited by intra-MRN microinfusion of DiMeC7 depends upon the integrity of 5HT neurons (14,15).

The objectives of the present series of experiments were 1) to determine if lesions, with 6-hydroxydopamine (6OHDA), of DA cell bodies in the VTA or DA terminals in the NAS, would attenuate the motor activity increases seen following ICV infusions of DiMeC7; and 2) to investigate the role of mesolimbic DA system in mediating the hyperactivity induced by intra-MRN infusions of DiMeC7 as well as the $GABA_A$ agonist, muscimol. The latter was accomplished through the use of the haloperidol and subsequently with 6OHDA lesions of the NAS.

Our results suggest that ICV infusions of DiMeC7 increase motor activity through at least two possible DA-mediated mechanisms; one involving the VTA-NAS DA pathway and the other originating in the MRN but not involving the NAS.

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METHOD

Animals

Male Sprague-Dawley rats (Olac, Bicester, UK; Sasco-King, Orange, WI) weighing 275–360 g at the time of surgery were used. Animals were housed individually in illumination- (12-hr light-dark cycle, lights on at 07:00 hr), temperature- (22 ± 2°C) and humidity- (50 ± 5%) controlled facilities. Food and water were available ad lib.

Cannulae Implantation

Bilateral cannulae were implanted under Equithesin anaesthesia (3.0 ml/kg; IP) using a technique described previously (5). Guide cannulae (23 gauge) were implanted 1.0 mm above the desired site for microinjection. The coordinates for the injection needles (30 gauge) were: ICV (0.4 mm posterior to bregma, ±2.0 mm lateral to midline, 3.1 mm below skull); VTA (3.4 mm posterior to bregma, ±0.7 mm lateral to midline, 7.4 mm below skull); NAS (3.5 mm anterior to bregma, ±1.7 mm lateral to midline, 8.4 mm below skull). Incisor bar was set at 5.0 mm above the interaural line. Coordinates for injections into the MRN were identical to those used previously (14). Animals were allowed one week to recover from surgery before behavioral testing.

Microinfusion Procedure

Drugs were microinfused in conscious unrestrained rats in 1.0 μl volumes into the VTA and MRN, and in 5.0 μl volumes ICV. Administration of drugs occurred over a 2.0-min period with the injection needles left in place for a further minute to allow for drug diffusion.

6OHDA Lesions

Destruction of DA cell body and terminal regions was achieved using 6OHDA-HBr (Sigma) in ascorbic acid (0.2 mg/ml). Bilateral lesions of the VTA were made with 6OHDA (6.0 mg/ml) in a 1.0 μl volume given over a 2-min period using a Harvard infusion pump. Bilateral lesions of the NAS were made with 6OHDA (12.0 mg/ml) in a 1.0 μl volume given under the same conditions. The monoamine oxidase inhibitor, pargyline (50 mg/kg; IP) and the noradrenergic uptake inhibitor, desmethylimipramine (DMI; 20 mg/kg; IP) were given to all animals 30 min prior to lesioning. Control subjects received ascorbic acid infusions.

Behavioral Testing

Independent groups of rats were used in each of the studies to be described below. Animals were handled daily after surgery to accustom them to the experimenter. One week after surgery the rats were allowed to habituate to the locomotor recording apparatus for 1.0 hr. This procedure was repeated prior to drug administration. The test sessions were performed between 09:00 and 16:00 hr in a lit room.

Behavioral Apparatus

Animals used in VTA and ICV studies were tested in photocell cages (40 × 25 × 25 cm) described previously (7). Rats used in MRN experiments were tested in cylindrical (46 cm diameter × 42 cm high) photocell chambers (LVE model #PAC-001). In both devices motor activity was calculated by the number of beam interruptions which were recorded automatically on computer.

Histology

On completion of each study subjects were killed and cannulae placements were assessed in cresyl violet stained tissue sections. Only data from rats with correct implantations were analysed.

Tissue Dissection

Brain areas used for high performance liquid chromatography (HPLC) were removed rapidly after decapitation and dissected over ice. Samples were then stored at −70°C until assayed.

HPLC Analysis

Samples were extracted on alumina and assayed for DA and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), using HPLC (25 mm column: C18, 5 mM Spherisorb 50DS2: column temperature: 35°C; mobile phase: phosphate buffer, pH 3.45, degassed with helium; flow rate: 0.8 ml/min) with electrical detection (Bioanalytical Systems LC-4 detector, +0.65 V). Assay sensitivity for DA and DOPAC was 10 pg/μl. Protein estimation was performed using the method of Lowry *et al.* (13). The tissue weights of the NAS and striatum were 26 ± 2 mg and 53 ± 4 mg respectively.

Drugs

Substance P (CRB, Cambridge, UK) and DiMeC7 (Peninsula, Belmont, CA) were dissolved in vehicle, artificial cerebrospinal fluid (CSF). Haloperidol (Searle), pargyline (Sigma), DMI (Sigma), amphetamine (Sigma) and muscimol (Research Biochemicals) were all dissolved in the systemic vehicle, saline (0.9%).

Statistics

Data were analysed using a one-way analysis of variance with a subsequent post hoc Newman-Keuls test, using two-tailed significance tables. A p level less than 0.05 was considered to be statistically significant.

RESULTS

Effect of 6OHDA Lesions of the VTA on Motor Activity Induced by ICV Microinfusions of DiMeC7

Ten days after bilateral 6OHDA lesions of the VTA rats were infused with DiMeC7 (4.0 μg) into the lateral ventricles. These lesions were found to attenuate, but not abolish, the hyperactivity observed after ICV administration of DiMeC7 (Fig. 1). HPLC analysis of the projection areas of the VTA revealed that the lesions were effective (Table 1).

Effect of 6OHDA Lesions of the NAS on Motor Activity Induced by ICV Microinfusions of DiMeC7

Lesions of the NAS with 6OHDA have been previously shown to reduce amphetamine-induced hyperactivity (12). Due to the large size of the NAS it was important to check that our lesions could also attenuate amphetamine-induced motor activity. Peripheral injections of amphetamine (1.2 mg/ml/kg; IP) were used to elevate spontaneous locomotor activity in control animals. Similar treatments in lesioned rats showed a reduced amount of activity (Fig. 2). Such lesions also blocked the motor response of DiMeC7 (4.0 μg) infused into the lateral ventricles (Fig. 3).

In an additional study (data not shown), the possibility that amphetamine administration could alter the motor response to subsequent microinfusions of DiMeC7 (4.0 μg) was investigated. Amphetamine (1.2 mg/ml/kg; IP), given 2.0 hr prior to DiMeC7

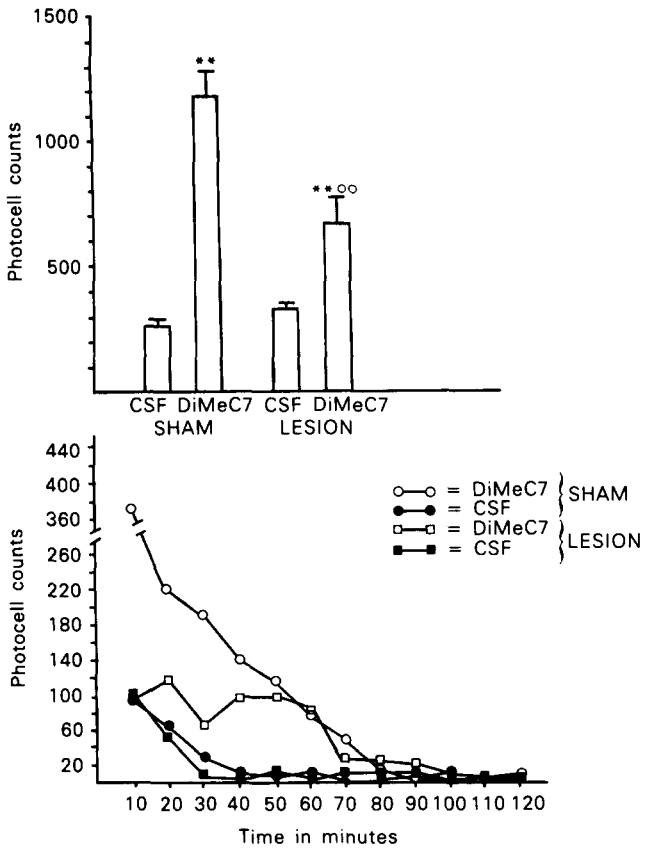

FIG. 1. Effect of bilateral 6OHDA lesions of the VTA on motor activity induced by ICV microinfusion of DiMeC7 (4.0 μg). (a) Mean cumulative photocell counts over the 2.0-hr test session. (b) Time course of action for each group over the 2.0-hr test session. **Represents $p<0.01$ with respect to vehicle-treated sham-lesioned group. OOrepresents $p<0.01$ with respect to DiMeC7-infused sham-lesioned group. N = 6 per group.

(4.0 μg) infusions (VTA or ICV), had no effect on the motor activity induced by the peptide analog. This is in slight contrast to an earlier report that pretreatment of SP into the VTA potentiated subsequent amphetamine treatment (23).

In a separate experiment multiple injections of DiMeC7 (4.0 μg) into the VTA (spaced 2 hr apart) did not show any attenuation of the second dose (data not shown) and therefore rule out any tachyphylaxis-like activity in our studies.

Effect of Haloperidol on DiMeC7 and Muscimol-Induced Locomotor Activity After Infusion Into the MRN

The dopamine antagonist, haloperidol (0.2 mg/ml/kg; IP), was used to block the motor activity induced by both DiMeC7 (1.0 μg) and muscimol (0.1 μg) given into the MRN. It was found that haloperidol selectively blocked the neurokinin-induced motor response without affecting the muscimol activity (Fig. 4).

Effect of 6OHDA Lesions of the NAS on DiMeC7 and Muscimol-Induced Locomotor Activity

Lesions of the NAS with 6OHDA were found to attenuate the motor activity induced by amphetamine (1.2 mg/ml/kg; IP), but had no effect on the locomotor response following infusion of DiMeC7 (1.0 μg) or muscimol (0.1 μg) into the MRN (Fig. 5).

TABLE 1

BIOCHEMICAL EFFECTS FOLLOWING LESIONS OF THE CELL BODY (VTA) OR TERMINAL (NAS) REGIONS OF THE MESOLIMBIC DOPAMINE PATHWAY

Study/Area	Group	DA	DOPAC
(A)			
NAS	Sham	4.84 ± 0.53	1.51 ± 0.25
	Lesion	0.27 ± 0.11*	0.40 ± 0.13*
Striatum	Sham	8.81 ± 0.43	1.30 ± 0.13
	Lesion	8.90 ± 0.68	0.94 ± 0.05
(B)			
NAS	Sham	5.46 ± 0.53	1.79 ± 0.35
	Lesion	0.91 ± 0.23*	0.22 ± 0.04*
Striatum	Sham	7.80 ± 0.50	1.10 ± 0.15
	Lesion	7.13 ± 0.64	0.72 ± 0.15
(C)			
NAS	Sham	6.45 ± 0.34	1.11 ± 0.06
	Lesion	0.91 ± 0.23*	0.22 ± 0.04*
Striatum	Sham	8.92 ± 0.25	1.12 ± 0.09
	Lesion	7.63 ± 0.28†	0.51 ± 0.08†

(A) Biochemical data following 6OHDA lesions of the VTA (n = 6).
(B) Biochemical data following 6OHDA lesions of the NAS (n = 6), amphetamine study (Fig. 5).
(C) Biochemical data following 6OHDA lesions of the NAS (n = 7–10), MRN, DiMeC7 and muscimol study (Fig. 5).
*Represents $p<0.01$. †Represents $p<0.05$ with respect to sham group. All results are given ± s.e. in μg/g wet weight of tissue.

The HPLC analyses confirmed that the lesions were effective (Table 1).

DISCUSSION

A major difficulty encountered when using neuropeptides in research is their rapid degradation. Development of synthetic peptide analogs has overcome this problem (1, 17, 19). In preliminary studies we have investigated the behavioral activity of various SP analogs, SP-methyl ester, SP-DAE and DiMeC7, at equimolar doses following ICV infusion. DiMeC7 had the largest

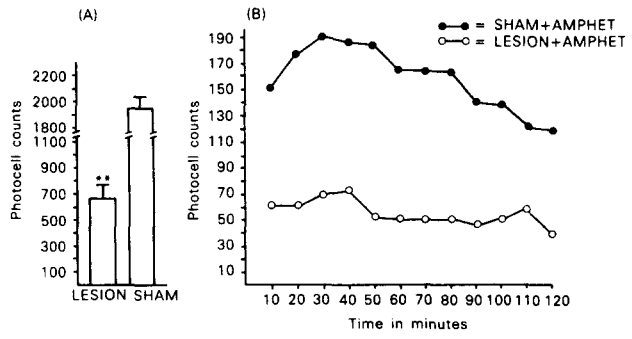

FIG. 2. Effect of bilateral 6OHDA lesions of the NAS on amphetamine-(1.2 mg/kg; IP) induced locomotor activity. (A) Mean cumulative photocell counts over the 2.0-hr test session. (B) Time course of action for each group over the 2.0-hr test session. **Represents $p<0.01$ with respect to lesioned group. N = 12 per group.

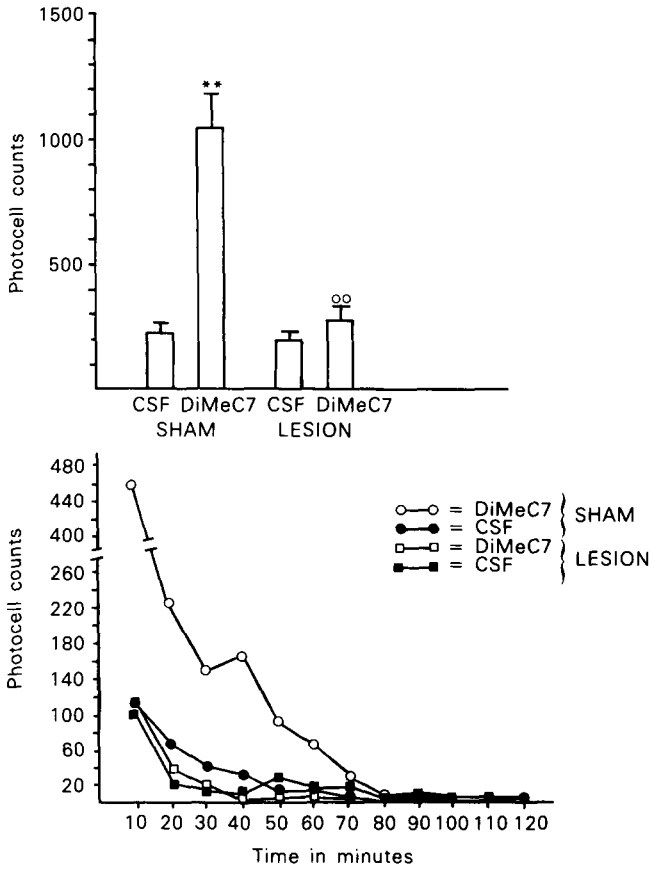

FIG. 3. Effect of bilateral 6OHDA lesions of the NAS on DiMeC7 (4.0 μg) induced motor activity. (a) Mean cumulative photocell counts over the 2.0-hr test session. (b) Time course of activity of each group over the 2.0-hr test session. **Represents $p<0.01$ with respect to vehicle-treated sham-lesioned group. OOrepresents $p<0.01$ with respect to DiMeC7-treated sham-lesioned group. N = 6 per group.

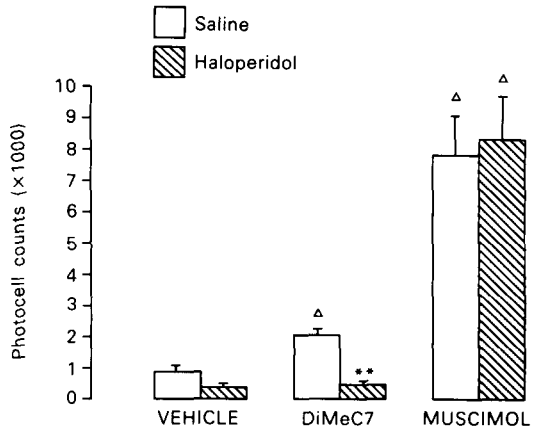

FIG. 4. Effect of haloperidol (0.2 mg/kg; IP) on locomotor activity induced after DiMeC7 (1.0 μg) and muscimol (0.1 μg) MRN infusions. Results are given as mean cumulative photocell counts derived from a 1.0-hr test session. **Represents $p<0.01$ with respect to the DiMeC7-treated group. ΔRepresents $p<0.01$ with respect to vehicle-treated group. N = 7–10 per group.

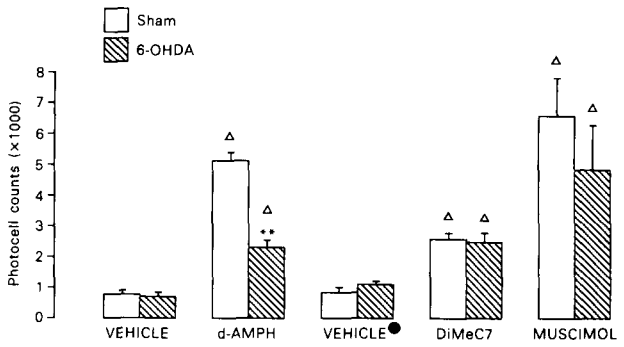

FIG. 5. Effect of bilateral 6OHDA lesions of the NAS on motor activity induced after infusions of DiMeC7 (1.0 μg) and muscimol (0.1 μg) into the MRN or amphetamine (1.2 mg; IP) during a 1.0-hr test session. 'Vehicle' refers to MRN-infused vehicle, whereas 'Vehicle●' refers to IP-injected animals. Results are given as mean cumulative photocell counts. **Represents $p<0.01$ with respect to sham-lesioned group. ΔRepresents $p<0.01$ with respect to vehicle-treated group. N = 7–10 per group.

effect on locomotor activity (data not shown) and was therefore used in the present studies.

Data obtained from ICV infusions of DiMeC7 show that it increases locomotion through activation of structures other than the VTA. Such a route of administration permits wide access for drugs to interact with many brain areas including the NAS and MRN. Both are known to contain SP receptors (21). Indeed, in the present study, infusion of DiMeC7 into the MRN did increase motor activity which agrees with earlier reports (14–16). Elevated activity observed after DiMeC7 infusions into the MRN could be blocked by haloperidol but not by 6OHDA lesions of the NAS. These results suggest that DiMeC7-induced hyperactivity, after MRN administration, utilizes a DA component at some later stage which would appear not to be located within the NAS. The motor output from the MRN which is involved in the DiMeC7 response is not yet defined. However, involvement of serotonin (5HT) neurons, within the MRN, in the DiMeC7 effect have been shown previously (16). Such 5HT cells innervate many areas within the CNS such as the medial habenula (22), many of which contain DA receptors (20) at which haloperidol could act (24). Furthermore, the habenula is known to have many connections with other CNS areas that are involved in motor control, such as the VTA (25,26), and as such might therefore play a pivotal role in the expression of DiMeC7-induced hyperlocomotion.

A direct action of DiMeC7 on SP receptors within the NAS is also possible. Direct microinfusions of SP into this nucleus have been reported to increase motor activity (10). In our present studies, 6OHDA lesions of the NAS were able to completely block the motor effects of ICV infusions of DiMeC7 suggesting that the NAS is involved in the expression of the effect. However, this result does not distinguish between direct or indirect activity of DiMeC7 on cells within the NAS. As to why lesions of the NAS but not the VTA block the DiMeC7-induced hyperactivity following ICV administration is not understood. One explanation could be that the VTA lesions caused some destruction of non-DA cells which counterbalance the motor effects of DA cell activation in the VTA-NAS pathway. Alternatively, the 6OHDA lesion of the VTA was not complete enough to block the DiMeC7-induced response.

An alternative site of action for DiMeC7 could be proposed in the periphery or spinal cord. However, ICV infusions of DiMeC7 do not elicit the classical 'pain response' seen after intrathecal injections of SP (18). Passage of DiMeC7 into the cerebrovasculature is also possible, where it might act as an irritant and thus induces elevated motor activity. This route has been suggested for

another gut-brain neuropeptide, cholecystokinin (2). Administration of intraperitoneal DiMeC7 (80 μg) did not produce any changes in locomotion following such studies (data not shown) and so it is unlikely that a peripheral site of action is responsible for the motor effects of ICV administered DiMeC7.

Earlier studies have assumed that ICV infusions of DiMeC7 have involved activation of the DA pathway from the VTA to the NAS. The present data clearly show that this is not entirely true and results from other studies would now seem to support our hypothesis. Firstly, it is known that ICV or VTA administration of SP can elevate motor activity (7,11). However, injections of SP at sites greater than 0.5 mm from the VTA were without effect (11). As most of the VTA is more than 0.5 mm from the ventricular system, ICV infusions of SP are unlikely to induce hyperactivity via a direct action on DA cell bodies in the VTA. Secondly, DiMeC7 has been shown to increase locomotor activity after ICV and VTA administration and yet only microinfusions into the VTA have been found to elevate DA metabolites within the NAS (6). This discrepancy between the two routes would tend to indicate that, after ICV infusion, DiMeC7 elevates motor activity through a route that does not involve activation of the mesolimbic DA system. This latter result also rules out the possibility that DiMeC7, the enzymatically stable SP analog, activates sites at some distance from the ventricular system.

In conclusion, it has been shown that the synthetic SP analog, DiMeC7, can elicit hyperactivity following microinfusion into the lateral ventricles of the rat. This response is also observed after MRN microinfusions. The exact neuronal pathways involved in each instance are, as yet, undetermined.

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