ELSEVIER

European Journal of Pharmacology 272 (1995) 119–121

ejp

Short communication

Influence of NMDA receptor ligands on thyrotropin-releasing hormone-induced scratching in rabbits

Patrizia Popoli *, Maria Grazia Caporali, Arsenia Scotti de Carolis

Pharmacology Department, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy

Received 4 August 1994; revised MS received 14 November 1994; accepted 15 November 1994

Abstract

The influence of intracaudate administration of *N*-methyl-D-aspartic acid (NMDA) and of the competitive NMDA receptor antagonist, DL-2-amino-5-phosphonovaleric acid (AP-5) was studied on thyrotropin-releasing hormone (TRH)-induced scratching in rabbits. NMDA (28 nmol) significantly increased the latency of TRH-induced scratching but did not modify the duration of this behaviour. Conversely, AP-5 (0.5 μmol) significantly potentiated scratching duration. Since TRH-induced scratching has been reported to be a dopamine-dependent behaviour, these results suggest that NMDA receptor ligands modulate dopaminergic neurotransmission.

Keywords: NMDA (*N*-methyl-D-aspartate); TRH (thyrotropin-releasing hormone); Dopamine; Striatum; (Rabbit)

1. Introduction

Thyrotropin-releasing hormone (TRH) has been reported to induce excitation and stereotyped behaviour in different animal species. Evidence suggests that the stimulatory effects of TRH are mainly mediated by a facilitatory influence on the dopaminergic system (see Popoli and Caporali, 1993). In rabbits, the behavioural effects induced by the intracerebroventricular (i.c.v.) injection of TRH were significantly antagonized by both dopamine D_1 and D_2 receptor antagonists (Popoli et al., 1989, 1991). Furthermore, TRH has been reported to stimulate striatal dopamine release (Kreutz et al., 1990). Taken together, these data strongly suggest that TRH-induced stereotypy may be regarded as a dopamine-dependent behaviour.

Dopaminergic (nigrostriatal) and glutamatergic (corticostriatal) pathways closely interact at the striatal level. Much evidence suggests that drugs acting at the *N*-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor modulate striatal dopaminergic functions. NMDA has been reported to influence striatal dopamine release (Carrozza et al., 1992; Imperato et al., 1990; Martìnez-Fong et al., 1992), while both competitive and non-competitive NMDA receptor antagonists induce dopamine-like stereotyped behaviour in rats (Schmidt and Bury, 1988; Sagratella et al., 1991).

The aim of the present work was to verify whether NMDA and DL-2-amino-5-phosphonovaleric acid (AP-5), a competitive NMDA receptor antagonist, could modulate the stereotyped behaviour (namely scratching) induced by TRH in rabbits.

2. Materials and methods

2.1. Surgical procedure

Male adult rabbits (2.3–2.5 kg) were used. Under pentobarbital anaesthesia, two 27-gauge needle cannulas were stereotaxically inserted into the ventriculus lateralis and the nucleus caudatus. Coordinates from bregma, sagittal suture and dura were as follows: A = +1.5; L = +1.6; V = −8 mm (ventriculus lateralis); A = −1.5; L = +3; V = −9 mm (nucleus caudatus). The experiments started 5–6 days thereafter. Injections were made with Hamilton syringes. The right placement of intracerebroventricular (i.c.v.) and intracaudate (i.c.) cannulas was verified by post-mortem examination.

* Corresponding author. Fax 6-4440053.

Elsevier Science B.V.
SSDI 0014-2999(94)00701-2

2.2. Behavioural observation

The animals were settled in a Plexiglas rectangular container (58 × 39 × 30 cm high) 30 min before starting the experiments. Mean latency of scratching (appearance of the first scratching bout), and mean scratching duration (total time spent scratching in minutes, from the first up to the last scratching bout), were recorded blind for each animal.

In separate experiments, the influence of various doses of AP-5 or NMDA administered alone into the caudate nucleus was tested in 3–4 animals/dose.

2.3. Drugs

All drugs were dissolved in saline. The injection volume was 10 μl. Intracaudate injections (NMDA, AP-5 or saline) were made 10 min before the i.c.v. administration of TRH.

3. Results

The behavioural effects induced by i.c.v. TRH (300 nmol/10 μl) in rabbits were described previously (Popoli et al., 1991, 1993). Stereotyped scratching was the most prominent and the best measurable component of TRH-induced behaviour.

The i.c. injection of NMDA alone did not induce marked behavioural effects up to the dose of 28 nmol. Higher doses (50–60 nmol) induced tremors and increased alertness. At doses of 140 nmol, clonic convulsions appeared. In NMDA (28 nmol i.c.) plus TRH-treated animals, the mean latency of scratching was significantly increased, while no significant effects on scratching duration were observed (Table 1).

AP-5, injected alone up to the dose of 1 μmol i.c., induced sniffing, licking and biting. A higher dose (2 μmol), also induced ataxia. In AP-5 (0.5 μmol i.c.) plus TRH-treated animals, the mean scratching duration was significantly increased (Table 1).

Table 1
Influence of NMDA and AP-5 on TRH-induced scratching in rabbits

Intracaudate treatments (+i.c.v. TRH)	Scratching mean latency (min ± S.E.M.)	Scratching mean duration (min ± S.E.M.)
Saline	3.5 ± 1	9.3 ± 1.7
AP-5 50 nmol	4.5 ± 1.8	9.8 ± 2.9
AP-5 0.5 μmol	4.3 ± 2.9	17.6 ± 4.7 [a]
NMDA 7 nmol	6.3 ± 3.1	8.3 ± 3.9
NMDA 28 nmol	13.3 ± 2.3 [a]	9.6 ± 3.5

Each group was composed of 6 animals. Intracaudate treatments were done 10 min before the i.c.v. injection of TRH.
[a] $P < 0.001$ vs. saline, according to one-way analysis of variance followed by Dunnett's test.

4. Discussion

The present results show that NMDA, injected into the caudate nucleus, significantly increased the latency to appearance of scratching in TRH-treated rabbits. Even though no significant effects were observed with respect to scratching duration, this would reflect an inhibitory influence of NMDA on TRH-induced behaviour. Since TRH-induced scratching may be regarded as a dopamine-dependent effect (see Introduction), the finding of an inhibitory influence of NMDA on this behaviour seems to disagree with the reports of a facilitatory influence of NMDA on striatal dopamine release (Carrozza et al., 1992; Martìnez-Fong et al., 1992). It should be noted, however, that the dopamine-releasing properties of NMDA have been reported at mM concentrations (Carrozza et al., 1992) or after infusion with Mg^{2+}-free solutions (Martìnez-Fong et al., 1992), but not at lower concentrations in normal Ringer (Imperato et al., 1990). In addition, intrastriatal NMDA induced hypomotility in rats, leading to the suggestion that NMDA receptor activation could counteract striatal dopaminergic function (Schmidt and Bury, 1988). With the present experimental conditions, the problem was complicated by the fact that NMDA was tested versus the effects induced by TRH. Even though the behavioural effects of TRH, especially stereotypy, seem to depend mainly on dopaminergic mechanisms, this drug has been reported to also affect neurotransmitter systems other than dopamine. It has been hypothesized that, at least in rats, TRH-induced scratching mainly depends on the activation of opiate receptors (Van Wimersma Greidanus et al., 1988). However, even though the mechanism of action of TRH is still under debate, and several neurotransmitters are likely to be involved in its effects, a major involvement of the dopamine system in TRH-induced scratching in rabbits has been clearly demonstrated (Popoli et al., 1989, 1991).

In the present experiments, the NMDA receptor antagonist, AP-5, significantly potentiated the duration of TRH-induced scratching in rabbits. These findings agree with the observation that both non-competitive (dizocilpine) and competitive (AP-5) NMDA receptor antagonists stimulate striatal dopamine release (Imperato et al., 1990; Moghaddam and Gruen, 1991). In addition to their presynaptic effects, NMDA receptor antagonists have been shown to stimulate locomotion in catecholamine-depleted mice (Carlsson and Carlsson, 1989), as well as in 6-hydroxy-dopamine-lesioned rats (Ouagazzal et al., 1994). Also, AP-5 induced behavioural effects similar to those elicited by dopamine receptor agonists after either intrastriatal or systemic administration to rats (Sagratella et al., 1991; Schmidt and Bury, 1988). It should be noted, however, that the present potentiating effects of AP-5 on TRH action, as

well as its facilitatory influence on dopamine release, occur only at quite high doses (Moghaddam and Gruen, 1991). This would make questionable the specificity of AP-5 as an NMDA receptor antagonist in such conditions. Moreover, a partial agonist activity of AP-5 on NMDA receptors has been proposed (Carrozza et al., 1992). Under our exprimental conditions, however, AP-5 had an effect on TRH-induced scratching different from that of NMDA, thus suggesting that its effects were actually mediated by an antagonistic activity at NMDA receptors. Furthermore, NMDA receptor blockade has been reported to selectively potentiate dopamine D_1 receptor-mediated behaviours (Morelli et al., 1992), and – although both dopamine D_1 and D_2 receptor subtypes seemed to be involved – the stimulation of dopamine D_1 receptors appears to be crucial for the appearance of TRH-induced scratching (Popoli et al., 1989, 1991).

Although our results do not allow the certainty that a direct connection between NMDA and TRH exists, they show that the modulation of striatal NMDA receptors significantly influences TRH-induced scratching in rabbits. Since experimental evidence showed that TRH-induced stereotypy is mainly – even if not exclusively – dependent on dopaminergic mechanisms, the present results also support the hypothesis that NMDA receptor antagonists may stimulate striatal dopaminergic neurotransmission.

References

Carlsson, M. and A. Carlsson, 1989, The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice, J. Neural Transm. 75, 221.

Carrozza, D.P., T.N. Ferraro, G.T. Golden, P.F. Reyes and T.A. Hare, 1992, In vivo modulation of excitatory amino acid receptors: microdialysis studies on *N*-methyl-D-aspartate-evoked striatal dopamine release and effects of antagonists, Brain Res. 574, 42.

Imperato, A., M.G. Scrocco, S. Bacchi and L. Angelucci, 1990, NMDA receptors and in vivo release in the nucleus accumbens and caudatus, Eur. J. Pharmacol. 187, 555.

Kreutz, M.R., I.N. Acworth, H. Lenhert and R.J. Wurtman, 1990, Systemic administration of thyrotropin-releasing hormone enhances striatal dopamine release in vivo, Brain Res. 536, 347.

Martìnez-Fong, D., M.G. Rosales, J.L. Gòngora-Alfaro, S. Hernandez and J. Aceves, 1992, NMDA receptor mediates dopamine release in the striatum on unanesthetized rats as measured by brain microdialysis, Brain Res. 595, 309.

Moghaddam, B. and R.J. Gruen, 1991, Do endogenous excitatory amino acids influence striatal dopamine release?, Brain Res. 544, 329.

Morelli, M., S. Fenu, A. Pinna and G. Di Chiara, 1992, Opposite effects of NMDA receptor blockade on dopaminergic D_1- and D_2-mediated behaviour in the 6-hydroxydopamine model of turning: relationship with c-fos expression, J. Pharmacol. Exp. Ther. 260, 402.

Ouagazzal, A., A. Nieoullon and M. Amalric, 1994, Locomotor activation induced by MK-801 in the rat: postsynaptic interactions with dopamine receptors in the ventral striatum, Eur. J. Pharmacol. 251, 229.

Popoli, P. and M.G. Caporali, 1993, Adenosine receptor agonists inhibit TRH-induced behaviour in rabbits: evidence for a main role of striatal A_2 receptors, Behav. Brain Res. 57, 105.

Popoli, P., M.G. Caporali and A. Scotti de Carolis, 1989, Effects of SCH 23390 on thyrotropin-releasing hormone-induced behaviour in rabbits, Eur. J. Pharmacol. 173, 211.

Popoli, P., M.G. Caporali and A. Scotti de Carolis, 1991, Interactions between dopamine D_1 and D_2 receptors in the model of thyrotropin-releasing hormone (TRH)-induced behaviour in rabbits, Eur. J. Pharmacol. 201, 11.

Sagratella, S., A. Scotti de Carolis, A. Pèzzola and P. Popoli, 1991, Behavioural and electroencephalographic interactions between haloperidol and PCP/sigma ligands in the rat, Psychopharmacology 105, 485.

Schmidt, W.J. and D. Bury, 1989, Behavioural effects of *N*-methyl-D-aspartate in the anterodorsal striatum of the rat, Life Sci. 43, 545.

Van Wimersma Greidanus, T.J.B., C. Maigret, G.J.E. Rinkel, P. Metzger, M. Panis, F.E.M. Van Zinnicq Bergmann, P.J.I.M. Poelman and D.L. Colbern, 1988, Some characteristics of TRH-induced induced grooming behavior in rats, Peptides 9, 283.