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Dopamine-independent and adenosine-dependent mechanisms involved in the effects of *N*-methyl-D-aspartate on motor activity in mice

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Abstract

The involvement of dopamine and adenosine mechanisms in the motor effects of systemically administered *N*-methyl-D-aspartate (NMDA) was studied in non-reserpinized and in reserpinized mice. In non-reserpinized mice NMDA induced motor depression (with 8, 25 and 75 mg/kg i.p.) during the first hour and motor activation (with 25 and 75 mg/kg i.p.) during the second hour after its administration. The non-selective adenosine antagonist, theophylline (3, 10 and 30 mg/kg i.p.), induced motor activation during both 1-h periods of observation. NMDA-induced motor depression in non-reserpinized mice was antagonized by theophylline. Higher doses of theophylline were needed to counteract the motor depressant effect induced by higher doses of NMDA. The motor activation induced by NMDA and theophylline in non-reserpinized mice was not additive and theophylline did not enhance the motor activation induced by high doses of NMDA. Both NMDA (25 and 75 mg/kg i.p.) and theophylline (10 and 30 mg/kg) induced motor activation in reserpinized mice and, when coadministered, NMDA counteracted the effect of theophylline. NMDA (8 and 25 mg/kg i.p.) antagonized and theophylline (3, 10 and 30 mg/kg i.p.) potentiated the motor activation induced by the non-selective dopamine agonist, apomorphine (0.1 mg/kg s.c.), in reserpinized mice. In reserpinized mice, the non-selective dopamine antagonist, haloperidol (0.5 mg/kg s.c.), antagonized the motor activation induced by apomorphine (0.1 mg/kg s.c.) and that induced by theophylline (10 mg/kg i.p.) and did not modify NMDA-induced motor activation. The present results suggest the existence of two different mechanisms in the elicitation of motor activity: a dopamine-independent NMDA-mediated mechanism, which is not modulated by adenosine, and a dopamine-dependent adenosine-modulated mechanism. NMDA-induced adenosine release might provide a connection between both mechanisms.

Keywords: NMDA (*N*-methyl-D-aspartate); Theophylline; Motor activity; Reserpine; (Mouse)

1. Introduction

Much experimental evidence supports the existence of antagonistic interactions between adenosine and *N*-methyl-D-aspartate (NMDA) receptors in the brain. Adenosine receptor stimulation has been shown to antagonize the excitotoxic effects of NMDA, probably through both presynaptic and postsynaptic mechanisms (Dragunow and Faull, 1988; Rudolphi et al., 1992). Presynaptically, adenosine and adenosine analogues are powerful inhibitors of glutamate release (Fastbom and Fredholm, 1985; Dolphin and Archer, 1983). Postsynaptically, the stimulation of adenosine receptors apparently limits the activity-evoked membrane depolarization, preventing the removal of Mg^{2+} blockade of the NMDA receptor-operated ion channel (Schubert et al., 1992). Both presynaptic and postsynaptic mechanisms seem to be mediated by adenosine receptors of the A_1 subtype (Dragunow and Faull, 1988; Rudolphi et al., 1992). Furthermore, NMDA receptor stimulation has been described to release endogenous adenosine (Hoehn and White, 1990; Chen et al., 1992; Pazzagli et al., 1994), which can be a protective endogenous mechanism to avoid NMDA-induced excitotoxic effects (Rudolphi et al., 1992).

We have recently shown that the systemic administration of NMDA to mice induces motor depression with low doses and, with high doses, this initial depressant effect is followed by a dose-dependent increase in

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motor activity (Ferré et al., 1994a). Similar findings have been reported by Von Lubitz et al. (1993), who described motor depression with low doses and motor activation with high doses of NMDA. These authors suggested that the motor depression induced by NMDA could be due to its ability to release adenosine, as stimulation of adenosine receptors induces a pronounced motor depression, most probably through an interaction with dopamine neurotransmission (for review, see Ferré et al., 1992).

Adenosine agonists inhibit, and adenosine antagonists potentiate, the toxic effects of exogenously administered NMDA (Finn et al., 1991; Von Lubitz et al., 1993), most probably through a postsynaptic adenosine-NMDA interaction. Therefore, a similar interaction could influence the NMDA-induced motor activation. The present work only provided evidence for the involvement of a presynaptic adenosine-NMDA interaction in the motor effects of systemically administered NMDA.

2. Materials and methods

2.1. Animals

Male mice of the OF1 strain, weighing 25–31 g, were used. The animals were allowed to adjust to a room with a 12-h light/dark cycle and 22 ± 2°C temperature. They had free access to food and water up to the time of measurement of motor activity. The mice were used only once.

2.2. Motor activity recording

The motor activity of groups of three mice ($n = 1$) (Andén and Grabowska-Andén, 1988) was recorded with a video-computerized system (Videotrack 512, View Point, Lyon, France) by using a subtraction image analysis. The system was set to measure any kind of motor activity (locomotion, rearing, intense grooming, jumps) and to avoid monitoring of very small movements (breathing, non-intense grooming, tremor). Four open field cages (35.5 × 35.5 × 35.5 cm) were simultaneously recorded in a sound-proof, temperature-controlled (22 ± 2°C) experimental room, which was uniformly illuminated with two incandescent lamps (100 W) located 2 m above the floor. Motor activity was recorded immediately after the animals, either reserpinized (one 1-h period of observation) or non-reserpinized (two 1-h periods of observation), were placed in the open-field cages without any adjustment period.

2.3. Drugs

Reserpine (Sigma, St. Louis, MO, USA) and haloperidol (RBI, Natick, MA, USA) were dissolved in a drop of glacial acetic acid which was made up to volume with 5.5% glucose. *N*-Methyl-D-aspartic acid (Sigma) was dissolved in 5.5% glucose and adjusted to pH 7.4 with NaOH. Theophylline (Sigma) and apomorphine hydrochloride (Sigma) were dissolved in 5.5% glucose. Reserpine (5 mg/kg s.c.) was administered 20 h and haloperidol (0.5 mg/kg s.c.) was administered 30 min prior to motor activity recording. Apomorphine (0.1 mg/kg s.c.), theophylline (3, 10 and 30 mg/kg i.p.) and *N*-methyl-D-aspartic acid (8, 25 and 75 mg/kg i.p.) were administered just before motor activity recording. The volume of injection was always 10 ml/kg.

2.4. Statistical analysis

All values (amount of time in seconds) recorded per 10 min were transformed (square root of (counts + 0.5)) (Andén and Grabowska-Andén, 1988) and analyzed by the 'summary measures' method (Matthews et al., 1990), by using the mean of all the transformed data per 3 mice ($n = 1$) as the summary statistic and by using either Student's non-paired *t*-test, a bifactorial analysis of variance (ANOVA) or one-way ANOVA with post-hoc Newman-Keuls comparisons to analyze differences among groups.

3. Results

3.1. Effect of the combined administration of NMDA and theophylline on the motor activity of non-reserpinized mice

The effect of the combined administration of four different doses of NMDA (0, 8, 25 and 75 mg/kg) and four different doses of theophylline (0, 3, 10 and 30 mg/kg) during the first and second hours after their administration was analyzed separately (for the first and second hour periods of observation) with a bifactorial ANOVA. During the first hour after administration NMDA induced a significant decrease (ANOVA: $P < 0.0001$) and theophylline a significant increase (ANOVA: $P < 0.0001$) in motor activity (Fig. 1, upper graph). As a significant interaction (ANOVA: $P < 0.01$) between the effect of both treatments was found, the different theophylline-treated groups were analyzed with one-way ANOVA. All doses of NMDA significantly decreased motor activity without the coadministration of theophylline; theophylline 3 and 10 mg/kg counteracted the depressant effect of NMDA 8 mg/kg; theophylline 30 mg/kg counteracted the motor depression induced by NMDA 25 mg/kg (statistical significances are shown in Fig. 1, upper graph).

During the second hour after their administration both NMDA and theophylline induced a significant increase in motor activity (ANOVA: $P < 0.0001$ in

both cases) (Fig. 1, lower graph). A significant interaction between both treatments was also found (ANOVA: $P < 0.001$) and the different theophylline-treated groups were also analyzed with one-way ANOVA. NMDA 25 and 75 mg/kg significantly increased motor activity without coadministration of theophylline; the motor activity induced by theophylline 10 mg/kg plus NMDA 25 mg/kg was not significantly different from that induced by theophylline 10 mg/kg; the motor activity induced by theophylline 30 mg/kg plus NMDA 25 or 75 mg/kg was not significantly different from that induced by theophylline 30 mg/kg (statistical significances are shown in Fig. 1, lower graph). No preconvulsant ('wild running') or convulsant activity or deaths were observed with any dose of NMDA.

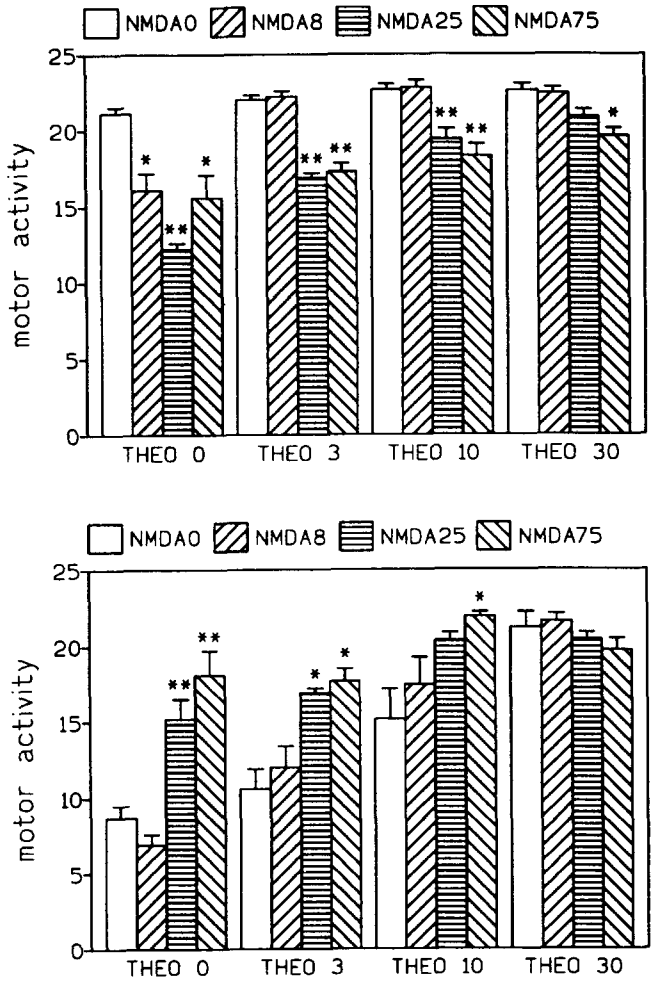

Fig. 1. Means ± S.E.M. of all 10-min transformed data per three mice ($n = 1$) from the first 1-h period (upper graph) and the second 2-h period of observation (lower graph) of non-reserpinized mice ($n = 4$–6/group). NMDA0, NMDA8, NMDA25 and NMDA75: NMDA 0, 8, 25 and 75 mg/kg i.p., respectively. THEO0, THEO3, THEO10 and THEO30: theophylline 0, 3, 10 and 30 mg/kg i.p., respectively. For each differently theophylline-treated group, * and **: significantly different (ANOVA, $P < 0.05$ and $P < 0.01$, respectively) compared to the respective NMDA0 group.

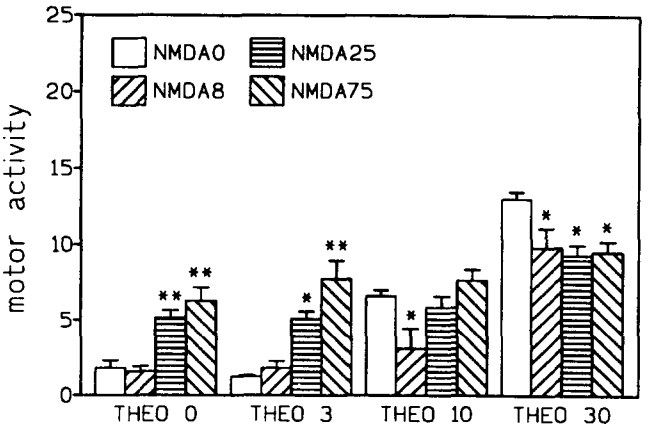

Fig. 2. Means ± S.E.M. of all 10-min transformed data per three mice ($n = 1$) from the first 1-h period of observation of reserpinized mice ($n = 4$–6/group). NMDA0, NMDA8, NMDA25 and NMDA75: NMDA 0, 8, 25 and 75 mg/kg i.p., respectively. THEO0, THEO3, THEO10 and THEO30: theophylline 0, 3, 10 and 30 mg/kg i.p., respectively. For each differently theophylline-treated group, * and **: significantly different (ANOVA, $P < 0.05$ and $P < 0.01$, respectively) compared to the respective NMDA0 group.

3.2. Effect of the combined administration of NMDA and theophylline on the motor activity of reserpinized mice

The effect of the combined administration of four different doses of NMDA (0, 8, 25 and 75 mg/kg) and four different doses of theophylline (0, 3, 10 and 30 mg/kg) during the first hour after their administration was analyzed by means of a bifactorial ANOVA. Both NMDA and theophylline induced a significant increase in motor activity (ANOVA: $P < 0.0001$ in both cases) (Fig. 2). A significant interaction between both treatments was found (ANOVA: $P < 0.0001$) and the different theophylline-treated groups were analyzed with a one-way ANOVA: NMDA 25 and 75 mg/kg induced motor activation without coadministration of theophylline; the motor activation induced by theophylline 10 mg/kg was counteracted by NMDA 8 mg/kg; the motor activation induced by theophylline 30 mg/kg was counteracted by NMDA 8, 25 and 75 mg/kg (statistical significances are shown in Fig. 2). No preconvulsant ('wild running') or convulsant activity or deaths were observed with any dose of NMDA.

3.3. Effect of NMDA and theophylline on the apomorphine-induced motor activation in reserpinized mice

NMDA 8 and 25 mg/kg significantly antagonized and theophylline 3, 10 and 30 mg/kg dose dependently enhanced the motor activity induced by apomorphine 0.1 mg/kg (one-way ANOVA; statistical significances are shown in Fig. 3). NMDA 75 mg/kg did not antagonize apomorphine-induced motor activation. However,

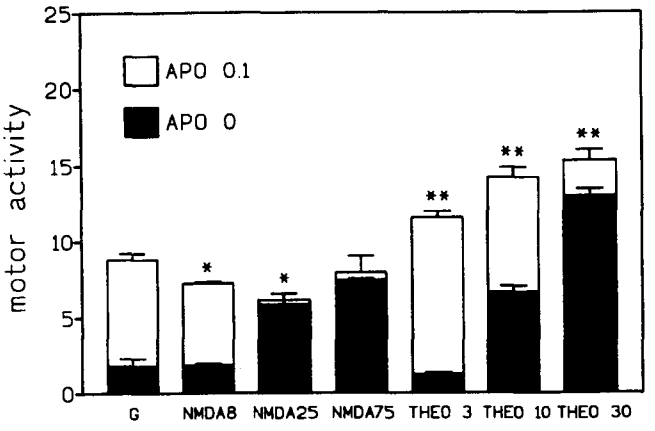

Fig. 3. Means ± S.E.M. of all 10-min transformed data per three mice ($n = 1$) from the first 1-h period of observation of reserpinized mice ($n = 4$–6/group). G: glucose; NMDA8, NMDA25 and NMDA75: NMDA 8, 25 and 75 mg/kg i.p., respectively. THEO3, THEO10 and THEO30: theophylline 3, 10 and 30 mg/kg i.p., respectively. APO0 and APO0.1: apomorphine 0 and 0.1 mg/kg s.c., respectively. For the groups treated with apomorphine 0.1 mg/kg, * and **: significantly different (ANOVA, $P < 0.05$ and $P < 0.01$, respectively) compared to the G group.

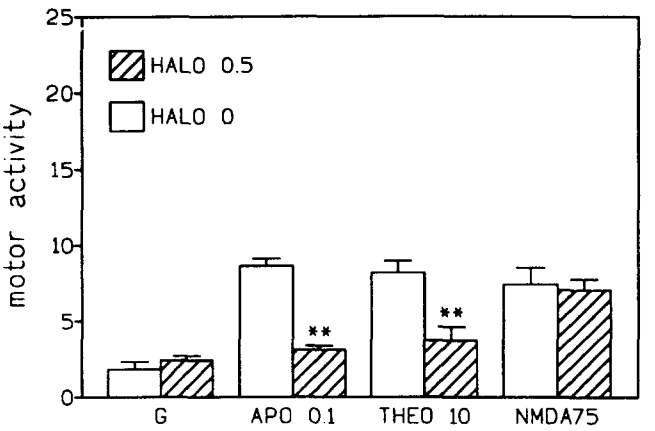

Fig. 4. Means ± S.E.M. of all 10-min transformed data per three mice ($n = 1$) from the first 1-h period of observation of reserpinized mice ($n = 4$–6/group). G: glucose; APO0.1: apomorphine 0.1 mg/kg s.c.; THEO10: theophylline 10 mg/kg i.p.; NMDA75: NMDA 75 mg/kg i.p.; HALO0 and HALO0.5: haloperidol 0 and 0.5 mg/kg s.c., respectively. **Significantly different (Student's non-paired t-test, $P < 0.01$ in all cases) compared with the respective HALO0 groups.

the motor activation induced by NMDA 75 mg/kg was about the same as that induced by apomorphine 0.1 mg/kg (Fig. 3).

3.4. Effect of haloperidol on the motor activation induced by apomorphine, theophylline and NMDA in reserpinized mice

Haloperidol 0.5 mg/kg significantly antagonized the motor activation induced by apomorphine 0.1 mg/kg and theophylline 10 mg/kg in reserpinized mice (Student's non-paired t-test: $P < 0.01$ in both cases). On the other hand, the NMDA-induced motor activation in reserpinized mice was not significantly modified by haloperidol (Fig. 4).

4. Discussion

As previously described (Ferré et al., 1994a), the systemic administration of NMDA to non-reserpinized mice induced motor depression with low doses (during the first hour after its administration), followed by an

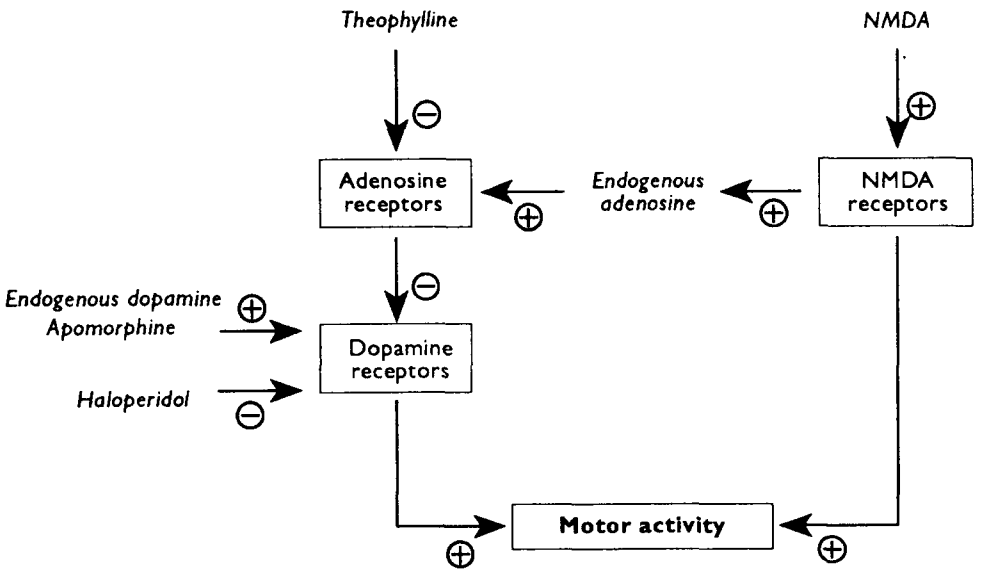

Fig. 5. Scheme of the two hypothetical mechanisms involved in motor activation described in the text: a dopamine-independent NMDA-mediated mechanism, which is not modulated by adenosine, and a dopamine-dependent adenosine-modulated mechanism. NMDA-induced adenosine release might provide a connection between the two mechanisms (see text).

increase in motor activity with higher doses (during the second hour after its administration). Although it has been claimed that the motor effects induced by the central administration of NMDA represent preconvulsant effects (O'Neill et al., 1989), no preconvulsant ('wild running') or convulsant activity was observed with the doses of NMDA used in the present study (both in reserpinized and non-reserpinized mice). In non-reserpinized mice, the non-selective adenosine antagonist, theophylline, induced, as has already been described (Snyder et al., 1981), an increase in motor activity and, in the present work, was found to counteract the motor depressant effect of NMDA. Higher doses of theophylline were needed to counteract higher doses of NMDA. Furthermore, a low dose of theophylline (3 mg/kg), which itself did not increase motor activity, did antagonize the motor depressant effect of a low dose of NMDA (8 mg/kg). These results strongly suggest that NMDA induces motor depression by an adenosine-mediated mechanism, probably related to the already described adenosine release induced by NMDA (Hoehn and White, 1990; Chen et al., 1992; Pazzagli et al., 1994).

The increase in motor activity induced by NMDA and theophylline in non-reserpinized mice during the second hour after their administration was not additive and theophylline did not enhance the motor activation induced by high doses of NMDA. The lack of an additive effect of NMDA and theophylline could be explained by a common mechanism. However, another more plausible explanation would be that the two compounds act through different mechanisms to produce motor activation and that, in addition, NMDA counteracts the effect of theophylline, due to their opposite effects on adenosine receptors (Fig. 5).

We have recently reported that NMDA induces motor activation in reserpinized mice (Ferré et al., 1994a). NMDA produced motor activation even during the first hour after its administration, which suggests that reserpinization sensitizes the animal to the motor activating effects of NMDA. In fact, with the highest dose of NMDA (75 mg/kg), motor activity increased in the non-reserpinized and in the reserpinized mouse about 2- and 4-fold, respectively. Dopamine depletion or chronic dopamine receptor blockade has been shown to increase the motor activating properties of methylxanthines, like caffeine or theophylline, in rodents (Fuxe and Ungerstedt, 1974; Popoli et al., 1991; Ferré and Fuxe, 1992; Ferré et al., 1994b). In agreement, in the present work, theophylline induced motor activity in reserpinized mice and this effect was stronger than in non-reserpinized mice. With the highest dose of theophylline (30 mg/kg), motor activity increased in the non-reserpinized and in the reserpinized mouse by about 5- and 7-fold, respectively. When NMDA and theophylline were coadministered to the reserpinized animal, a clear counteraction of the theophylline-induced motor activity by NMDA was demonstrated, supporting the hypothesis of opposite actions of both compounds on adenosine receptors (Fig. 5). Also, these results suggest that a postsynaptic interaction between adenosine and NMDA receptors is not involved in the motor effects induced by NMDA (see Introduction). In that case, NMDA-induced motor activity should be potentiated by theophylline.

A postsynaptic antagonistic interaction between adenosine and dopamine receptors in the basal ganglia has recently been suggested to be a key mechanism of action responsible for the motor depressant effects of adenosine agonists and for the motor stimulant effects of adenosine antagonists (Ferré et al., 1991a,b,c, 1992, 1993). Through this interaction, stimulation of adenosine receptors (of the A_{2a} subtype) inhibits and their blockade potentiates the motor activity induced by dopamine receptor (of the D_2 subtype) stimulation (Ferré et al. 1991a,b). It was found that NMDA inhibited and theophylline potentiated the motor activation induced by the non-selective dopamine receptor agonist, apomorphine, in reserpinized mice. This is in agreement with the existence of a postsynaptic antagonistic adenosine-dopamine interaction and with the suggested adenosine-mediated mechanism of NMDA-induced motor depression (Fig. 5). A presynaptic antagonistic adenosine-dopamine interaction may also take place in the non-reserpinized mouse, with adenosine receptor stimulation inhibiting dopamine release (Popoli et al., 1994).

In reserpinized mice, the antagonistic effect of NMDA on apomorphine- and theophylline-induced motor activation was always limited by the motor activating effect of NMDA. For instance, the highest dose of NMDA (75 mg/kg) did not counteract the motor activation induced by theophylline 10 mg/kg or apomorphine 0.1 mg/kg, as at these doses the three compounds induced approximately the same motor activation. These results suggest that NMDA induces motor activation through a mechanism independent of that used by apomorphine and theophylline. In fact, in reserpinized mice, the non-selective dopamine receptor antagonist, haloperidol, blocked the motor activating effects of apomorphine and theophylline and did not modify NMDA-induced motor activity. The blockade by haloperidol of the theophylline-induced motor activation in reserpinized mice suggests that some endogenous dopamine is left after reserpinization.

It is proposed that the present results could most easily be explained by the scheme shown in Fig. 5. By means of the already described antagonistic adenosine-dopamine interaction, stimulation of adenosine receptors inhibits and their blockade (with adenosine receptor antagonists, like theophylline) potentiates, the stimulant effect of dopamine receptor stimulation (with

endogenous dopamine or with dopamine receptor agonists, like apomorphine) on motor activity. NMDA receptor stimulation induces motor depression by releasing endogenous adenosine, which stimulates adenosine receptors. Therefore NMDA receptor stimulation can counteract the motor stimulant effect of adenosine receptor antagonists and dopamine receptor agonists, and adenosine receptor antagonists can counteract the motor depressant effect of NMDA. Furthermore, NMDA receptor stimulation, differently to adenosine receptor blockade, induces motor activation through a mechanism independent of dopamine receptor stimulation.

NMDA has been reported to induce motor activation after its local administration in the striatum (mainly in the nucleus accumbens), in the hippocampus, in the substantia innominata and in the so called mesencephalic locomotor region (Donzanti and Uretsky, 1983; Yang and Mogenson, 1989; Milner and Mogenson, 1988; O'Neill et al., 1989; Shreve and Uretsky, 1991; Svensson et al., 1994). NMDA has been shown to induce dopamine release when locally infused in the rat striatum (although with high concentrations) (Imperato et al., 1990; Morari et al., 1994; Svensson et al., 1994). Therefore, it has been suggested that the motor activation induced by the local infusion of NMDA in the striatum is dopamine-mediated and related to its dopamine releasing properties (Svensson et al., 1994). We have previously hypothesized that the systemic administration of NMDA induces motor activity by acting in the striatum but at a level postsynaptic to dopamine terminals (Ferré et al., 1994a). However, the apparently absolute dopamine independence suggests that brain structures other than the striatum are involved in NMDA-induced motor activation. In conclusion, the present results suggest the existence of two different mechanisms in the elicitation of motor activity: a dopamine-independent NMDA-mediated mechanism, which is not modulated by adenosine, and a dopamine-dependent adenosine-modulated mechanism. NMDA-induced adenosine release might provide a connection between the two mechanisms.

Acknowledgements

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