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Stimulatory Effect of N-Methyl Aspartate on Locomotor Activity and Transmitter Release From Rat Nucleus Accumbens

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HAMILTON, M. H., J. S. DE BELLEROCHE, I. M. GARDINER AND L. J. HERBERG. *Stimulatory effect of N-methyl aspartate on locomotor activity and transmitter release from rat nucleus accumbens.* PHARMACOL BIOCHEM BEHAV 25(5) 943–948, 1986.—N-Methyl-aspartate (NMA), an agonist at central glutamate receptors, elicited prolonged and intense locomotor activity when injected into the nucleus accumbens septi (NAS) in subconvulsive doses (3–10 μg bilaterally). This effect was antagonised by intra-accumbens injection of the specific NMA antagonist, aminophosphonovaleric acid (APV) in a dose (3.0 μg bilaterally) that was without intrinsic effect when given on its own. Intra-accumbens injection of APV also suppressed locomotor hyperactivity elicited by intra-accumbens injection of DA (50 μg bilaterally) in rats pretreated with nialamide. *In vitro* release of [^{3}H]-acetylcholine in accumbens tissue slices was significantly increased in the presence of NMA (30 μM) or N-methyl-D-aspartate (NMDA) (15 μM). Both effects were antagonised by APV (30 μM). Similar results were obtained with tissue slices of rat corpus striatum. These results suggest that locomotor stimulation by intra-accumbens NMA is mediated by an action on the mesolimbic dopaminergic neuron, either directly or via a cholinergic interneuron. In addition, activity at the glutamate synapse may be enhanced by the presence of DA affecting glutamate release and/or reuptake.

Acetylcholine Nucleus Accumbens Dopamine Glutamate 6-Hydroxydopamine Locomotion DAPV, D-2-amino-5-phosphonovalerate NMDA, N-methyl-D-aspartate

THE nucleus accumbens septi (NAS) receives a diverse innervation from the ventral tegmental area, raphe nucleus, hippocampus, allocortex, neocortex and other parts of the brain [19]. Many of the transmitters present in the afferent pathways have been shown to have profound effects on the level of spontaneous locomotor activity when injected directly into the NAS. Thus, dopamine brings about a rise in locomotor activity, producing an especially powerful and long-lasting effect after pretreatment with a monoamine oxidase inhibitor, e.g., nialamide or pargyline [5,21]. Other dopamine agonists, e.g., 6,7-dihydroxy-1,2,3,4-tetrahydro naphthalene (ADTN) [31] and, to a lesser degree, apomorphine [17] also stimulate locomotor activity. Other afferent systems affecting locomotor activity include 5-hydroxytryptamine (5HT), which facilitates dopamine-stimulated locomotion [16,18] and GABA, which depresses it [18,23]. An intrinsic cholinergic system has also been shown to modulate activity [7,11], but its precise mode of action is uncertain, since the cholinergic neurone does not appear to receive an input from the DA projection [4,10], and it must presumably mediate the effects of some other afferent system.

Apart from the well established afferents to the NAS, a further major input is from the allocortex and hippocampus. The transmitter employed by this pathway is likely to be a dicarboxylic amino acid such as glutamate or aspartate since lesion of the fimbria/fornix decreases the high affinity uptake of glutamate in the NAS by 45%, and the levels of glutamate by 33% [30], while ablation of the frontal cortex reduces high affinity glutamate uptake by 18–25% [29]. Agonists of the three main types of glutamate receptor, N-methyl-D-aspartate (NMDA), kainate and quisqualate (see Fagg [15] for review) have each been found to stimulate locomotor activity when injected into the nucleus accumbens [13]. However, the selective involvement of specific receptors has not been established in earlier studies [22] and hence

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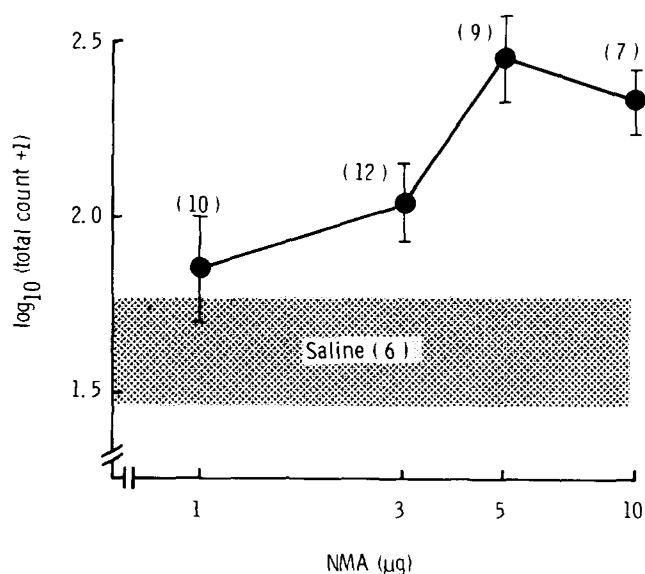

FIG. 1. Dose response curve for the effect of intra-accumbens NMA on spontaneous locomotor activity. Locomotor activity is expressed in arbitrary counts on a log scale for the 50 min period commencing 15 min after injection. Vertical bars indicate standard errors. Shaded area indicates the saline control score. Numerals in parentheses indicate sample size. Bilateral injections of NMA were given, each at the dose shown. The effect of NMA was significant (analysis of variance and covariance with repeated measures) at doses of 5 μg and 10 μg, $p<0.0002$ and 0.00033 respectively. A significant difference ($p<0.05$) at individual time points (repeated t-tests) was found at 20, 30, 40 and 50 min for 5 μg NMA and at 30, 40, 50 and 60 min for 10 μg NMA.

the present study was undertaken to characterise the action of NMDA in the nucleus accumbens using the selective NMDA antagonist, amino phosphonovaleric acid (APV). In addition, although the target cells mediating the effects of NMDA are not known, NMDA has been shown to stimulate the release of acetycholine in the neostriatum [26] and this possible mode of action in the NAS was investigated *in vitro*.

BEHAVIOURAL METHODS

Subjects and Apparatus

Stainless steel 22-gauge guide cannulae were implanted bilaterally under halothane anaesthesia in male Lister PVG rats (Banting & Kingman Ltd.) weighing 230–300 g at the time of operation. The cannulae were angled 10° towards the midline, entering the skull at a point 8.8 mm anterior to the vertical interaural plane and 2.3 mm lateral to the midline [12], and terminating 3.5 mm short of the intended site of injection. A 7-day period was allowed for recovery from surgery. Solutions were injected through a 28-gauge internal cannula terminating in the NAS at a point 7.0 mm below the skull surface. Injections were made in a volume of 1.0 μl delivered over a 30 sec period using a micrometer-driven Agla microsyringe, the inner cannula being left *in situ* for 1 min after completion of the injection. Cannula placements were verified on enlarged photographic projections of unstained frozen sections at the end of the experiment.

Locomotor activity was measured in enclosed circular bowls 35 cm in diameter, resting on a central pivot and six microswitches spaced about the perimeter [2]. Counts made by movement of the rat from one part of the bowl to another were recorded automatically at 5-min intervals and the strongly kurtotic distribution of scores was normalised by logarithmic transform, as in previous studies [2]. Postural and grooming movements without locomotion did not have an appreciable effect on the count.

Drugs

NMA (N-methyl-DL-aspartate) was dissolved in isotonic saline and adjusted to pH 7 by addition of NaOH. Intracranial administration of this compound commonly induces convulsions, and rats to be given NMA or its vehicle were therefore lightly anaesthetised with ether immediately before injection. They were then allowed 5 min for recovery before the commencement of testing, which continued for a further hour. APV (D-2-amino-5-phosphonovalerate) and DA were dissolved in isotonic saline containing ascorbate (1 mg/ml) and given by intracerebral injection. Nialamide was dissolved in isotonic saline and injected intraperitoneally in a volume of 1.0 ml/kg body weight. NMA and APV were obtained from Cambridge Biochemicals Ltd. and DA and nialamide were obtained from Sigma Chemical Co. Ltd.

Procedure

The rats were fully familiarised with the interior of the bowls and locomotor tests were carried out as follows:

Intra-accumbens NMA and locomotor activity. Each rat was injected with one of four doses of NMA, or saline in random order, at 48 hr intervals, and locomotor scores were recorded for 1 hr after injection.

APV and its interaction with NMA. Rats were given intra-accumbens injections at 48 hr intervals, in random order, of (1) saline, (2) APV (3.0 μg/μl/1 min) (without etherisation), and (3) either APV or saline, followed by NMA (3.0 μg/μl) 10 min later. Locomotor activity was measured for 1 hr after injection, as before.

APV and DA-induced hyperactivity. Rats were pretreated with nialamide (100 mg/kg IP) and injected intracerebrally 2 hr later with DA (20 μg/μl). After 1.5 hr, when hyperactive behaviour was fully established, the rats were injected with either APV (3 g/μl) or saline (1.0 μl), and locomotor activity was recorded for a further 3.5 hr.

Statistical analysis was carried out by analysis of variance and covariance with repeated measures (BM DP 2V).

BIOCHEMICAL METHODS

Male CFY rats (250 g body weight) were stunned, killed by cervical dislocation and the brains removed. Two coronal cuts were made at right angles to the axis of the brain, the first 1 mm rostral to the optic chiasma and the second at 1.5 mm rostral to the first cut. The nucleus accumbens was dissected out from this section using a rat brain atlas for reference. A second caudal slice was taken and the corpus striatum dissected from this section.

Tissue slices of nucleus accumbens (or corpus striatum) were cut in a plane parallel to the coronal section (0.35 mm thickness approximately) and immediately immersed in Krebs bicarbonate medium of the following composition (mM): NaCl, 118; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 1.2; $NaHCO_3$, 25; KH_2PO_4, 1.2; $CaCl_2$, 2.5; glucose, 11.1, pH 7.4 gassed with 95% O_2:5% CO_2. Tissue slices were first incubated in the presence of 0.06 μM (methyl-^{3}H)-choline chloride (78 Ci/mmol) at 37°C for 30 min. After preincubation in medium

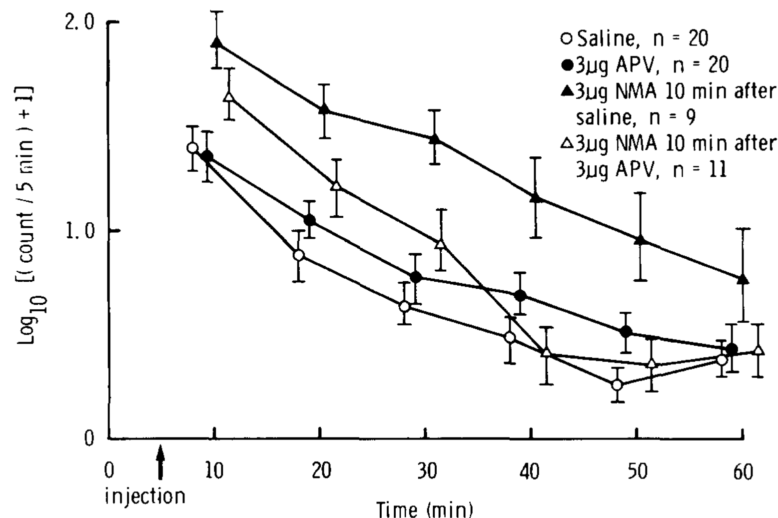

FIG. 2. Effect of APV on NMA stimulated locomotor activity. Lomomotor scores [log (counts/5 min) + 1] in consecutive 10 min periods after injection of NMA and APV separately and together and after control injection of saline. Data were analysed by repeated measures analysis of variance. NMA significantly enhanced activity ($p<0.0001$). Individual time points were analysed by repeated t-tests. The effect of NMA was significantly greater than vehicle at all time points up to and including 50 min ($p<0.01$). APV significantly reduced the effect of NMA at three time points. 30–50 min inclusive ($p<0.05$).

containing isotope the slices were transferred to a perspex block containing 8 tissue chambers and superfused with isotope-free Krebs bicarbonate medium maintained at 37°C, at a rate of 1 cm^3/min for a further 30 min to reach a steady baseline of release. Tissue slices were then transferred after the wash-out period to Krebs bicarbonate medium (1 ml) under control or test conditions, incubated for 10 min at 37°C and transferred to fresh medium containing 34 mM K^+ in the presence or absence of drugs as indicated for a further 5 min incubation period. At the end of incubation, tissue slices were removed and aliquots of media taken for analysis of tritium by liquid scintillation counting. Aquasol 2 (New England Nuclear Chemicals) was used as the scintillant. The tritium content of the tissue slices was also determined following solubilisation in Soluene 350 (Packard Instrument Company, Inc). Efflux of transmitter is expressed as the fractional release min^{-1}, i.e., the total amount released in each incubation period as a percentage of the total remaining in the tissue at the beginning of the time period divided by the time of incubation in minutes. Basal efflux rates have not been subtracted from the rates in the presence of K^+.

In this assay, [^{3}H]-choline is used as a precursor of [^{3}H]-ACh. In the presence of eserine it has been shown that the predominant [^{3}H]-labelled compound released by K^+-depolarisation during the conditions otherwise described above is [^{3}H]-ACh, [^{3}H]-choline being a minor component. In subsequent experiments, including this study where eserine is omitted, the K^+-evoked release of tritium is used as an index of the release of [^{3}H]-ACh. Incubation in the absence of eserine avoids any secondary effects on transmitter release through build-up of endogenous ACh for example. The rationale and assay procedure has been previously described in detail [8–10].

Statistical analysis of transmitter release was carried out by Student's t-test.

RESULTS

Effect of NMA and of APV on Locomotor Activity

Bilateral injections of NMA caused a dose-dependent and sustained increase in locomotor activity, first apparent in the 3-µg dose, and maximal at 5 µg (Fig. 1). No further increase in response was seen above 5 µg, possibly because of the onset of intermittent convulsive seizures that became increasingly frequent at doses higher than 5 µg. Locomotor scores generally underwent a progressive decline during the course of the 1 hr observation period (Fig. 2), but the stimulant effect of NMA (3 µg), relative to control injections, was present throughout the hour. Bilateral intra-accumbens injection of APV (3 µg) reduced or eliminated the stimulant effect of NMA (3 µg) injected 10 min later, whereas this dose of APV followed 10 min later by saline had no significant effect on locomotor activity.

Effect of APV on DA-Induced Hyperactivity

Strong and sustained hyperactivity was produced by bilateral intracranial injections of DA (20 µg) in rats pretreated with nialamide (100 mg/kg IP 2 hr before) (Fig. 3). Bilateral intra-accumbens injection of APV in the 90th min after injection of DA brought about a sharp decrease in hyperactivity, while control injections of saline were without effect. The inhibition of locomotor hyperactivity by APV was of relatively short duration (Fig. 3b, inset), and, within 20 min, scores had returned to their previous high levels which were then maintained for the remaining 3.5 hr of observation.

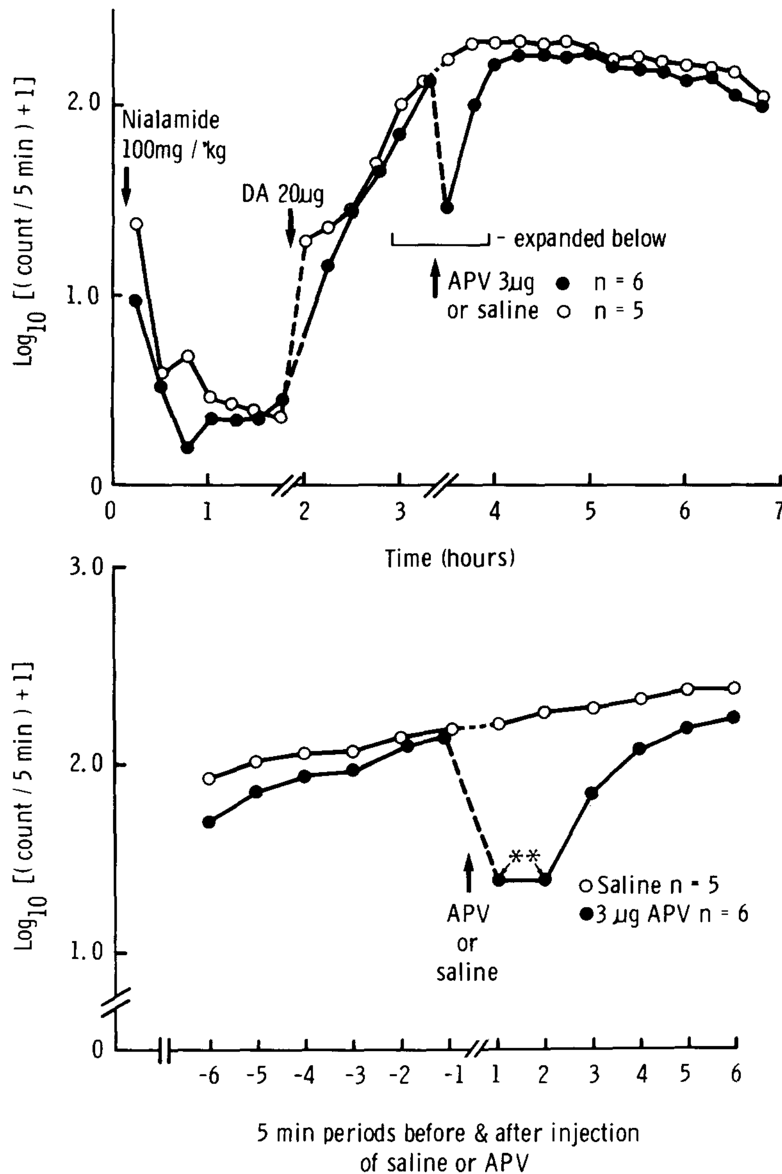

FIG. 3. Effect of APV on dopamine-stimulated locomotor activity. Locomotor activity [log (counts/5 min) + 1] in consecutive 15 min periods (upper part) in rats given successive bilateral intra-accumbens injections, at the intervals shown of dopamine (DA) and APV, or control injections of saline, after an initial injection of nialamide (IP). In the lower part, the locomotor scores recorded at 5-min intervals immediately before and after injection of APV (or saline) is shown. *Indicates that APV significantly ($p<0.05$) reduced the effect of DA (Student's t-test).

Effect of NMA on the Release of [³H]-Acetylcholine From Tissue Slices of Rat Nucleus Accumbens and Corpus Striatum

As has previously been reported for corpus striatum, the basal release of [^{3}H]-acetylcholine from tissue slices of rat nucleus accumbens is significantly increased by NMA (30 μM) and NMDA (15 μM). Both effects were significantly antagonised by the presence of APV (Table 1). A similar effect was also seen in this study in the corpus striatum in response to NMA (30 μM), which was antagonised by the presence of either 15 μM DAPV or 100 μM DLAPV (Table 2).

DISCUSSION

Stimulatory Effect of NMA on Locomotor Activity

The present study confirms previous reports that bilateral injection of NMA into the nucleus accumbens leads to hyperactivity [13,14] and also shows, for the first time, that the locomotor effects of NMA can be antagonised by the selective antagonist, APV. Donzanti and Uretsky [13] suggest that the NMA receptor may be less important for the regulation of locomotor activity than the kainate and quisqualate receptors because the maximal effect is lower. How-

TABLE 1

EFFECT OF N-METHYL-D-L-ASPARTATE (NMA) AND N-METHYL D ASPARTATE (NMDA) ON THE RELEASE OF [3H]-ACETYLCHOLINE FROM TISSUE SLICES OF RAT NUCLEUS ACCUMBENS

	Release of [3H]-acetylcholine fractional release/10 min		
	30 μM NMA		
Control	5.58 ± 0.20 (10)	6.57 ± 0.12 (10)	*$p<0.01$
10 μM APV	5.44 ± 0.61 (4)	5.58 ± 0.52 (4)	
30 μM APV	5.27 ± 0.36 (6)	5.20 ± 0.44 (6)	†$p<0.05$
	15 μM MDA		
Control	4.63 ± 0.05 (6)	6.33 ± 0.25 (6)	*$p<0.02$
30 μM DAPV	4.55 ± 0.27 (6)	4.80 ± 0.05 (6)	†$p<0.001$

Values are means ± SEMs.
*Indicates that NMDA significantly increased the release of [3H]-acetylcholine, †indicates that the effect of NMA or NMDA was significantly reduced by the presence of APV or DAPV.

TABLE 2

EFFECT OF N-METHYLASPARTATE (NMA) ON THE RELEASE OF [3H]-ACETYLCHOLINE FROM TISSUE SLICES OF RAT CORPUS STRIATUM

	Release of [3H]-acetylcholine		
	30 μM NMA		
Control	5.92 ± 0.12 (13)	7.44 ± 0.24 (13)	*$p<0.001$
15 μM DAPV	6.28 ± 0.33 (6)	6.69 ± 0.32 (5)	†$p<0.05$
27 μM DAPV	5.81 ± 0.13 (8)	6.69 ± 0.16 (8)	†$p<0.05$
Control	5.26 ± 0.16 (11)	6.39 ± 0.39 (11)	*$p<0.05$
30 μM DLAPV	5.24 ± 0.24 (7)	6.85 ± 0.63 (7)	
100 μM DLAPV	4.15 ± 0.30 (4)	4.66 ± 0.12 (4)	†$p<0.05$

*Indicates that NMA significantly increased the release of [3H]-acetylcholine and †indicates that the effect of NMA was significantly reduced by the presence of DAPV or DLAPV.

ever, although we have not tested kainate or quisqualate and cannot make a direct comparison, the increase in locomotion caused by NMA was considerable, giving locomotor counts almost as high as those evoked by DA itself. This does not seem to be an unimportant degree of locomotor facilitation. The potencies of NMA in both the present study and that of Donzanti and Uretsky [13] were similar, maximal measurable responses occurring at 5 and 3 μg respectively. In agreement with Donzanti and Uretsky [13] we observed that high doses of NMA produced convulsive seizures that disrupted organised motor activity. This occurred at doses of 10 μg in our study but 5 μg in those of Donzanti and Uretsky [13]. This slight difference may be related to the fact that we used an injection volume of 1 μl instead of 0.5 μl to give the same dose of NMA, the more dilute solution that we used would be less likely to elicit paroxysmal responses in the affected units.

Effect of APV on Dopamine-Stimulated Locomotor Activity

Further experiments were carried out to elucidate the site of action of NMA. One possible site of action could be through presynaptic glutamate receptors located on dopaminergic terminals, which by facilitating the release of DA could prolong the locomotor response. This type of mechanism, involving presynaptic muscarinic receptors, has been proposed to explain the rapid oxotremorine stimulation of dopamine-induced locomotor activity and release of DA in the accumbens [8,11]. Further, the nature of the locomotor behaviour induced by NMA resembles the hyperactivity induced by DA plus nialamide both in intensity and sustained character (greater than 30 min with NMA and greater than 5 hr with DA) rather than the transient response elicited by DA (alone) or apomorphine [18]. This indicates that endogenously released glutamate may contribute to the prolonged response to exogenous DA (plus nialamide) by prolonging the release of DA. This possibility was investigated by testing the effect of APV on DA-stimulated locomotor activity. The inhibitory effect that was obtained gave support to this proposal. The source of endogenous glutamate may be explained by the observation that DA inhibits glutamate uptake [20] and this would lead to its build up in the synapse. Glutamate uptake is the first step in the termination of its synaptic action and uptake inhibition would have the effect of prolonging its activity.

Further support for the suggestion that glutamate agonist action is mediated through a dopaminergic mechanism comes from studies with cis-Z-flupenthixol and fluphenazine which reverse the excitatory effects of NMA, quisqualate, kainate and the glutamate receptor agonist, [(R,S)-α-3-hydroxy-5-methyl-4-isoxazolepropionic acid] (AMPA) on locomotor activity and from the use of amine depletors (α-methyltyrosine and reserpine) which reduce the effect of AMPA and kainate [1,13]. Furthermore, glutamate has previously been shown to stimulate the release of [3H]-dopamine from tissue slices of rat striatum [16,25] and NAS [24].

The reduction of DA-induced locomotor activity by intra-accumbens injection of the glutamate antagonist, APV, might also suggest a role for glutamate at a site in the NAS downstream for the DA terminals. However, although spiroperidol- and sulpiride-binding sites are present on the corticostriate pathway [3, 28, 31], no evidence of dopamine regulation of glutamate release in the NAS has yet been demonstrated.

Effect of NMA on Cholinergic Cells

The possibility that the action of NMA may be mediated by receptors present on intrinsic cells in addition to receptors on dopaminergic terminals was also investigated. In this paper, we provide evidence that in the absence of Mg^{2+}, NMA and NMDA enhance the resting release of [3H]-ACh from cholinergic interneurones. The effect is similar to that already reported in neostriatum [26], and is reversed by APV. Further, the increased level of ACh release induced by NMA may facilitate on-going dopaminergic transmission since the cholinergic agonist, oxotremorine, enhances DA-stimulated locomotor activity [11] and K^+-evoked release of [14C]-dopamine [8].

If a cholinergic interneurone was involved in the behavioural response to NMA, it would be expected that a cholinergic antagonist would reduce the effect of NMA.

However, the biphasic effect of cholinergic agonists on locomotor activity, an early stimulation followed by a prolonged inhibitory phase, does not allow this hypothesis to be tested in this way (Hamilton, de Belleroche and Herberg, in preparation).

In conclusion, these results show that the glutamate agonist, NMA, stimulates locomotor activity which effect is reversed by the selective antagonist, APV. Two possible sites of action of NMA are indicated, the dopamine terminal and the intrinsic cholinergic cells present in the nucleus accumbens and both could contribute to the stimulatory effect of NMA on locomotor behaviour.

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