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Locomotor Response of Nialamide Pretreated Old Rats to Intraaccumbens Dopamine

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COUSIN, K. M., N. J. URETSKY AND M. C. GERALD. *Locomotor response of nialamide pretreated old rats to intraaccumbens dopamine.* PHARMACOL BIOCHEM BEHAV **22**(3) 461–468, 1985.—The objective of this study was to determine the locomotor activity response of young (6 month), mature (15 month), and old (26 month) rats to bilateral intraaccumbens injections of dopamine after pretreatment with nialamide. Young and mature rats responded to dopamine with high rates of activity, while old rats either did not respond at all or responded with a lower intensity of activity. In contrast, the response of old rats to dopamine or ergometrine alone or to dopamine after pargyline pretreatment was not less than that of mature and young rats. These results suggest that the attenuated response of old rats to dopamine after nialamide pretreatment is not due to a decrease in dopamine receptor activity, but appears to be due to some unique property of nialamide in these animals. However, the reduced response of old rats to dopamine was not due to the inability of nialamide to inhibit monoamine oxidase, since nialamide completely inhibited the activity of this enzyme in the nucleus accumbens of old rats.

Locomotor activity Dopamine Aging Monoamine oxidase Nucleus accumbens Nialamide

IMPAIRMENTS in motor function have been demonstrated in aged rats that appear to be related to changes in dopaminergic activity in the brain. Thus, aged rats display deficits in sensorimotor coordination [40] and swimming performance [23] that can be partially reversed by intrastriatal nigral grafts [11] or the administration of dopaminergic agonists [23] respectively. In addition, aged rats show a reduced rotational response to amphetamine or intrastriatally administered dopamine [8,18].

The motor deficits observed in aged rats occur concomitantly with age-related alterations in the biochemistry of the dopaminergic neurons of the nigrostriatal tract. Declines have been reported in striatal tyrosine hydroxylase activity [25], striatal dopamine synthesis [35], striatal dopamine uptake [15], and striatal dopamine levels [10,17]. In addition, decreases in striatal dopamine receptor binding [9, 17, 26, 37] and dopamine stimulated adenylate cyclase [12,36] have been described.

The nucleus accumbens, a forebrain component of the mesolimbic system, is thought to be involved in the initiation and regulation of spontaneous locomotor activity [27]. It has also been implicated in the pathophysiology of schizophrenia [21,39], Parkinson's disease [34] and Huntington's chorea [3], and in the antipsychotic actions of neuroleptics [1,4]. It has previously been demonstrated that this nucleus receives a prominent dopaminergic projection from the ventral tegmental area [20] and that bilateral intraaccumbens injections of dopamine produce a marked increase in locomotor activity [7, 14, 16, 22, 29, 30, 32] which can be blocked by neuroleptic drugs [5, 14, 22, 29, 31].

Because of its involvement in normal motor activity, the nucleus accumbens may also play a role in the decline in motor function observed in aged rats. For example, the rotational response of rats has been shown to require the nucleus accumbens [19] and as mentioned above the intensity of this response shows an age-related decline. The nucleus accumbens may also contribute to the reduced locomotor activity displayed by aged rats [11], and the age-related decline in swimming performance [23].

The present experiments were designed to examine dopamine receptor function in the nucleus accumbens of young (6 month), mature (15 month), and old (26 month) rats by measuring the locomotor response of these animals to bilateral intraaccumbens injections of dopamine after pretreatment with nialamide, a monoamine oxidase inhibitor. This procedure has been shown to produce an intense and long lasting stimulation of locomotor activity [6, 14, 22]. To determine whether the responses to dopamine are related to the nialamide pretreatment, the locomotor activity response of mature and old rats to dopamine after pretreatment with

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an alternative monoamine oxidase inhibitor (pargyline), to ergometrine alone (a dopamine agonist), or to dopamine alone was studied.

METHOD

Animals

Male F344 rats, 6, 15 and 26 months of age were used in these studies and housed in AALAC approved cages. Food (Purina Rat Chow) and water were available ad lib. The animal quarters were maintained on a 6 a.m.:6 p.m. light: dark cycle. Animals were permitted to acclimate to our laboratory environment for at least one week prior to experimentation.

Surgical and Injection Procedure

Rats were anesthetized with a halothane/oxygen mixture and secured in a stereotaxic frame (David Knopf Inst., CA). Holes were then drilled on each side of the skull at A+9.8, L±1.6, DeGroot coordinates [28]. Injections were made using a 10 μl Hamilton syringe (Hamilton Company, Reno NE) which was attached by a clamp to the electrode carrier of the stereotaxic apparatus. The needle tip was inserted through the holes to a depth of V−0.15, and the solution was injected at a rate of 0.5 μl/min. The needle was left in place for an additional minute to allow the solution to diffuse away from the needle tip and then withdrawn from the brain. Following bilateral injections, the skin incision was closed with a wound clip and covered with lidocaine to prevent any pain which might interfere with locomotion. Anesthesia was then discontinued and the rats were placed in individual activity cages for monitoring locomotor activity. Each animal was injected only once.

Locomotor Activity

Rats were placed in activity cages (Opto-Varimex-Minor, Columbus Inst., Cols., OH) and allowed to acclimate for 30 min. They were then removed from the cages and anesthetized with the halothane/oxygen mixture prior to receiving bilateral intraaccumbens drug injections. Following drug administration, rats were returned to their respective cages and locomotor activity recorded as a function of time. The activity cages were designed to measure ambulatory movements, but not total horizontal or total vertical movement. The cages contained 12×12 infrared beams passing at a height of 5 cm from the bottom of the cage through a ventilated Plexiglas box measuring 42 cm square and 20 cm high. Locomotor activity (i.e., ambulatory movement) was recorded as the number of times 2 consecutive beams, 3.5 cm apart, were interrupted during a 60 minute period. The data were recorded by a digital counter (Columbus Inst., Columbus, OH). Animals were observed visually for convulsions, tremors or other non-ambulatory behavior. Observations were made in an isolated environmental room maintained at 21±1°C under diffuse light, beginning at approximately 1100 on day 1 and ending at 0200 on day 2. Pretreatment, if given, was administered at 0930. Whenever possible, the locomotor responses of rats of all 3 ages were determined simultaneously.

Histology

Injection coordinates for intraaccumbens injections were verified in each rat following activity experiments. Rats were sacrificed and the brain excised and placed in 4.0% formaldehyde for 1–2 days. Frozen brain sections (40 μ thick) were sliced sequentially in a rostral to caudal direction using a Cryo-Cut Microtome (American Optical Corp., Buffalo, NY) until injection tracts were visible. The needle tracts (site of injection) were compared to the location of the nucleus accumbens (using the stereotaxis atlas of Pellegrino and Cushman, DeGroot coordinates) for correct injection placement in each animal.

Monoamine Oxidase Assay

Monoamine oxidase activity was determined in duplicate in nucleus accumbens homogenates [24]. The nucleus accumbens was dissected [13] and placed on dry ice. The nucleus was weighed and homogenized in 10 Vol of 0.001 M phosphate buffer, pH 7.0. 100 μl of buffer substrate containing 0.1 μl (3H)dopamine (30.4 Ci/mmol) in 0.1 M potassium phosphate, pH 6.75, was added to 20 μl of homogenate (2.0 mg of tissue), and incubated for 30 min at 38°C. The reaction was stopped by the addition of 10 μl of 3 N HCl. (3H)metabolites were extracted into 500 μl of ethyl acetate, and 200 μl of the ethyl acetate phase was transferred to a counting vial and (3H)metabolite concentration determined by liquid scintillation counting. Blanks contained 100 μl of buffer substrate and 20 μl of the buffer used to homogenize the tissue.

Drugs

The following drugs were obtained from Sigma Chemical Co., St. Louis, MO: nialamide, dopamine HCl, ergometrine HBr, and pargyline HCl. Dopamine and ergometrine were dissolved in nitrogen bubbled distilled water containing 0.1% sodium metabisulfite, and adjusted to pH 5.5–6.0 with 0.5 N NaOH. These solutions were injected into the nucleus accumbens in a volume of 0.5 μl as described under surgical and injection procedure. Control animals were injected with an equal volume of vehicle. Nialamide was dissolved in a minimum of 1.0 N HCl before the addition of an appropriate volume of double distilled water. Pargyline was dissolved in 0.9% NaCl. Intraperitoneal injections were administered in a volume of 1 ml/kg. ^{3}H-Dopamine was obtained from New England Nuclear Corporation, Boston, MA.

Statistics

Data is expressed as the mean and standard error of the mean (S.E.M.). Significant differences in locomotor activity and monoamine oxidase activity were evaluated using the two-tailed Student's t-test [38] with a level of $p<0.05$ being considered significant. An analysis of variance with Student Neuman-Keuls test for multiple comparisons was performed when determining significant differences in activity among young, mature and old rats.

RESULTS

Effect of Dopamine on the Locomotor Activity of Young, Mature and Old Rats Pretreated With Nialamide

Rats were pretreated with nialamide (100 mg/kg, IP) 1.5 hours prior to bilateral intraaccumbens injections of vehicle or various doses of dopamine. Figure 2 shows the mean locomotor activity of groups of nialamide pretreated young, mature, and old rats after intraaccumbens injections of vehicle. The locomotor activity of all 3 groups was much lower than

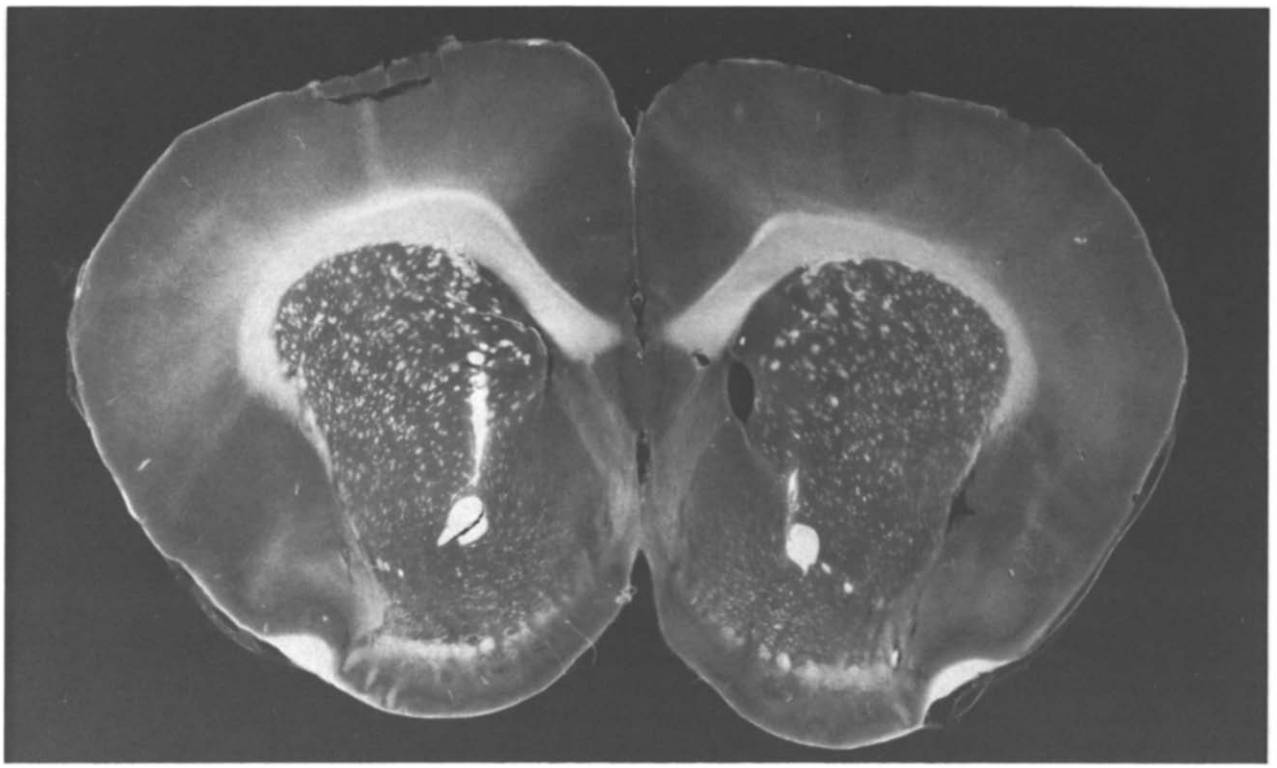

FIG. 1. Photomicrograph showing bilateral needle tracts terminating in the nucleus accumbens. Injection tracts were visible from A + 9.0 to A + 9.8 and were located at the site of or slightly medial to the anterior commissure and within the nucleus accumbens. This histological section is representative of sections from rats responding to bilateral injections of dopamine with high rates of locomotor activity.

that obtained after the intraaccumbens injection of dopamine (Note the 10 fold greater scale on the y axis in Fig. 3, the response to DA, compared to Fig. 2, the response to vehicle) with the activity of old and young rats being significantly lower than that of mature rats at several of the time intervals. In order to determine the locomotor activity response to the intraaccumbens administration of dopamine, the mean activity value for each age group, recorded after the intraaccumbens administration of vehicle, was subtracted from that obtained after the intraaccumbens administration of dopamine.

The bilateral administration of dopamine into the nucleus accumbens of young and mature rats pretreated with nialamide produced an intense and long lasting stimulation of locomotor activity (Fig. 3). This response to dopamine was dose dependent and, at all doses tested, was many times greater than the response to the intraaccumbens injections of the vehicle. The locomotor activity response of old rats to dopamine at doses of 2.5–20 μg was significantly lower than that of young and mature rats. At a 40 μg dose, the response of old rats was significantly lower than that of young rats only.

Effect of Dopamine on the Locomotor Activity of Mature and Old Rats That Were not Pretreated With a Monoamine Oxidase Inhibitor

In order to determine the response to dopamine in the absence of a monoamine oxidase inhibitor, mature and old rats were given bilateral intraaccumbens injections of dopamine (20 or 40 μg). As reported previously [29], the hypermotility response to dopamine in the absence of a monoamine oxidase inhibitor was brief, lasting approximately one hour. Both old and mature rats exhibited a hypermotility response to dopamine and there was a trend toward a greater response in the old rats (Table 1).

Effect of Ergometrine on the Locomotor Activity of Mature and Old Rats Which Were not Pretreated With a Monoamine Oxidase Inhibitor

To further characterize the response of mature and old rats to the intraaccumbens administration of direct acting dopamine receptor agonists, ergometrine (1 μg) was administered bilaterally into the nucleus accumbens of non-pretreated mature and old rats. In contrast to dopamine, and as reported by others [33], intraaccumbens administration of ergometrine produced a long lasting stimulation of locomotor activity (Fig. 4). The response of both mature and old rats was nearly identical.

Effect of Dopamine on the Locomotor Activity of Mature and Old Rats Pretreated With Pargyline

Mature and old rats were pretreated with pargyline (75 mg/kg, IP), a monoamine oxidase inhibitor, 1.5 hours prior to bilateral intraaccumbens injections of vehicle or dopamine (20 μg), and the locomotor activity was recorded. The locomotor activity of groups of mature and old rats after the administration of vehicle is shown in Fig. 5A, with old rats showing significantly greater activity at 2, 3, and 4 hours after vehicle injection. This baseline activity was subtracted

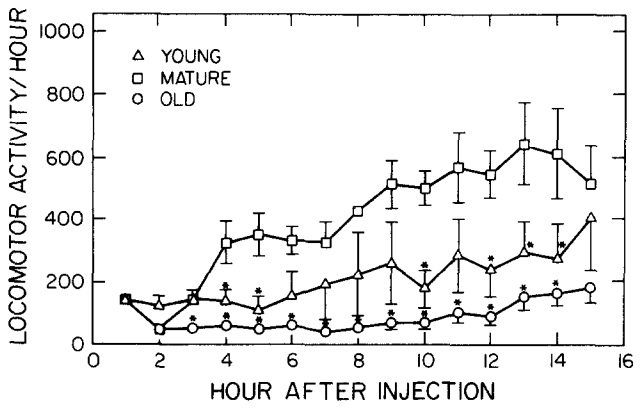

FIG. 2. Baseline locomotor activity of nialamide pretreated young, mature, and old rats injected with vehicle. Rats were injected with nialamide (100 mg/kg, IP) 1.5 hours prior to bilateral intraaccumbens injections of vehicle (0.5 μl). Motor activity was recorded at one hour intervals for 15 hours after vehicle injection. Each point represents the mean one hour activity±S.E.M. of 7 rats. Analysis of variance: $F(2,18)=4.54$, $p<0.05$, 3 hr; $F(2,18)=9$, $p<0.005$, 4 hr; $F(2,18)=10.75$, $p<0.001$, 5 hr; $F(2,18)=6.35$, $p<0.01$, 6 hr; $F(2,18)=3.63$, $p<0.05$, 7 hr; $F(2,18)=5.62$, $p<0.025$, 8 hr; $F(2,18)=6.25$, $p<0.01$, 9 hr; $F(2,18)=20.85$, $p<0.001$, 10 hr; $F(2,18)=5.91$, $p<0.025$, 11 hr; $F(2,18)=12.15$, $p<0.001$, 12 hr; $F(2,18)=6.39$, $p<0.01$, 13 hr; $F(2,18)=4.69$, $p<0.025$, 14 hr. Student Newman-Keul's test: *$p<0.05$ when compared to mature rats.

from the activity recorded after dopamine administration in order to obtain the hypermotility response to dopamine. Figure 5B shows that the intraaccumbens administration of dopamine produced a marked and prolonged hypermotility response in both mature and old rats pretreated with pargyline. In contrast to the effects after nialamide pretreatment, the intensity of the response to dopamine after pargyline pretreatment was not significantly different between the two age groups, and the time course of the response for these two age groups was nearly identical.

Effect of Nialamide and Pargyline on Monoamine Oxidase Activity in the Nucleus Accumbens of Mature and Old Rats

Groups of mature and old rats were injected intraperitoneally with either saline, nialamide, or pargyline in the doses used for the behavioral studies, and the monoamine oxidase activity in the nucleus accumbens of these animals was determined 5 hours after drug injection, using dopamine as a substrate. As shown in Table 2, old rats injected with saline showed a trend toward greater enzyme activity compared to mature rats ($0.05<p<0.1$). Nevertheless, both pargyline and nialamide completely inhibited monoamine oxidase activity in the nucleus accumbens of both mature and old rats (enzyme activity in either age group was not greater than blank after drug treatment).

DISCUSSION

Previous studies have reported deficits in the motor function of aged rats that have been associated with an impairment in dopaminergic neurotransmission in the corpus striatum [8, 11, 18]. However, other brain regions containing dopamine nerve terminals may be involved in producing these deficits. The nucleus accumbens, located in the ventral

TABLE 1

ONE HOUR LOCOMOTOR ACTIVITY RESPONSE OF MATURE AND OLD RATS TO INTRAACCUMBENS INJECTIONS OF DOPAMINE

Treatment	Locomotor Activity/Hour	
	Mature	Old
dopamine 20 μg	624 ± 173	1064 ± 256
dopamine 40 μg	744 ± 80	1001 ± 26*

Dopamine at doses of 20 μg/0.5 μl or 40 μg/0.5μl was injected bilaterally into the nucleus accumbens of groups of 4 rats. Activity was monitored for one hour following the central injections. Baseline activity (one hour activity of rats receiving intraaccumbens injections of vehicle, data not shown) was always subtracted from dopamine stimulated activity to get the locomotor activity response/hour. *Activity is statistically different from that of mature rats, $p<0.05$.

TABLE 2

DETERMINATION OF MONOAMINE OXIDASE ACTIVITY IN THE NUCLEUS ACCUMBENS OF MATURE AND OLD RATS INJECTED WITH NIALAMIDE OR PARGYLINE

	Monoamine Oxidase Activity (μmoles/g/hr) (Mean ± S.E.M.)		
	Saline	Pargyline	Nialamide
Mature	2.40 ± 0.23	N.D.	N.D.
Old	3.13 ± 0.22*	N.D.	N.D.

Mature and old rats were injected systemically with saline, nialamide (100 mg/kg, IP) or pargyline (75 mg/kg, IP) five hours prior to sacrifice. The nucleus accumbens was dissected and the activity of monoamine oxidase in each nucleus was determined in duplicate. Each value represents the mean enzyme activity in the nuclei of 3–4 rats ± S.E.M. N.D.=not detectable; activity was not above blank values. *Activity is not statistically different from that of mature rats ($0.05<p<0.10$).

forebrain, is known to be involved in the initiation and maintenance of locomotor activity and dopaminergic neurotransmission at this site plays an important role in the regulation of this behavior [27]. Thus, abnormal dopaminergic neurotransmission in the nucleus accumbens may be involved in the motor deficits of aged rats. The present study was designed to determine whether dopamine receptor function in the nucleus accumbens is altered in old rats compared to young and mature rats. Dopamine receptor function was measured using a standard procedure in which the locomotor activity response to dopamine was determined after its injection directly into the nucleus accumbens of rats pretreated with a monoamine oxidase inhibitor. This procedure has been shown to produce an intense and long lasting stimulation of locomotor activity [6, 14, 22].

In our initial studies, dopamine was injected into the nucleus accumbens of old, mature, and young rats after pretreatment with nialamide. Compared to the response of the rats from the other age groups, the response of old rats to dopamine was markedly reduced (Fig. 3). Thus, dopamine did not significantly stimulate the locomotor activity of old rats at doses of 2.5 and 5.0 μg, while it produced a marked stimulation of locomotor activity in young and mature rats at these doses. At higher doses (20 and 40 μg), dopamine did

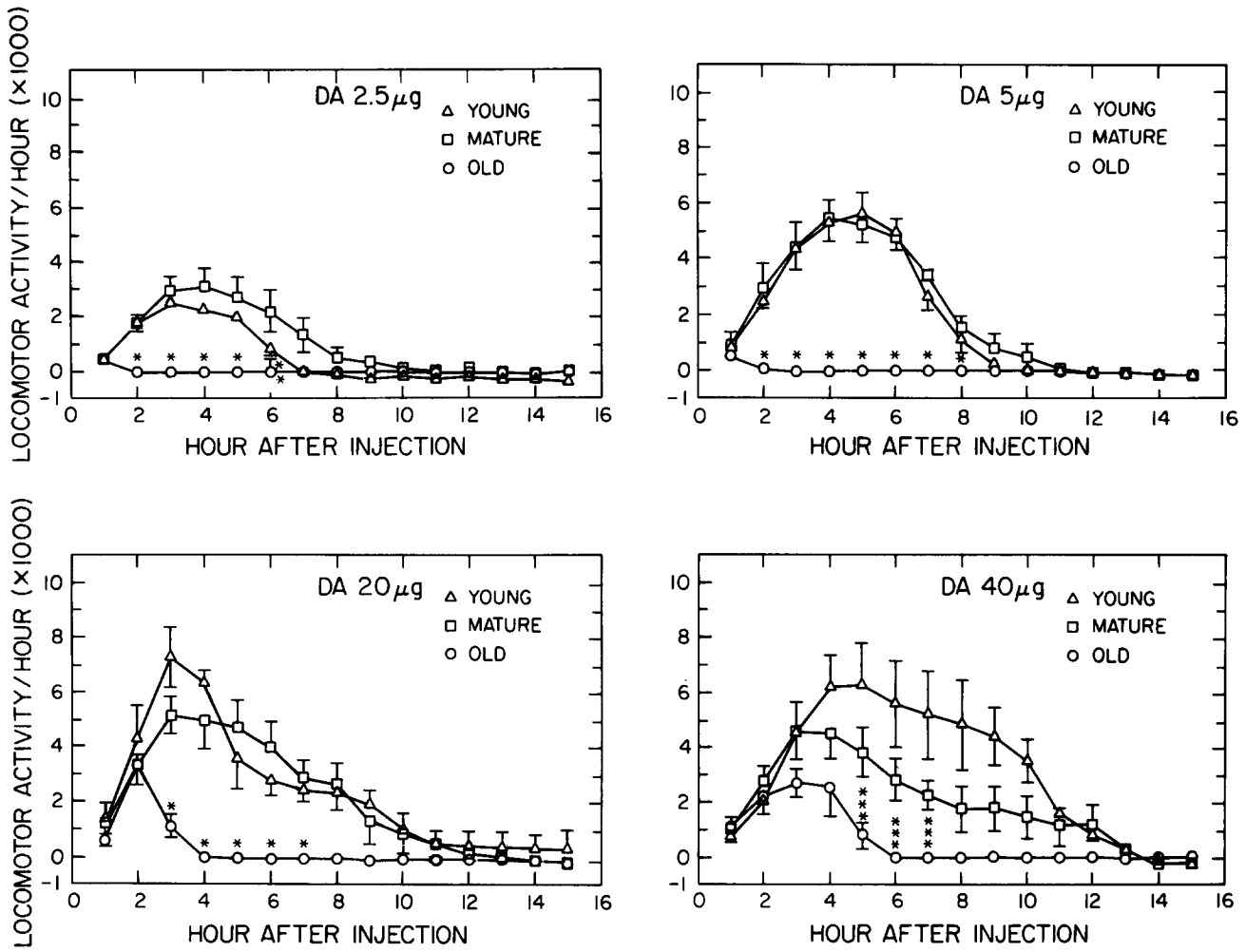

FIG. 3. Locomotor activity response of young, mature and old rats, pretreated with nialamide, to intraaccumbens injections of dopamine (DA). Rats were pretreated with nialamide (100 mg/kg, IP) 1.5 hours prior to bilateral intraaccumbens injections of different doses of dopamine (2.5 μg, 5.0 μg, 20 μg, and 40 μg/0.5 μl). Motor activity was recorded at 1 hour intervals for 15 hours after the injection of dopamine. Each point represents the mean one hour activity±S.E.M. of 3–6 rats. Baseline activity (nialamide + vehicle, Fig. 2) was always subtracted from activity recorded after the injection of dopamine to get the locomotor activity response/hour. Analysis of variance, DA 2.5 μg: $F(2,8)=12.39$, $p<0.005$, 2 hr; $F(2,8)=23.88$, $p<0.001$, 3 hr; $F(2,8)=15.39$, $p<0.005$, 4 hr; $F(2,8)=9.86$, $p<0.01$, 5 hr; $F(2,8)=5.35$, $p<0.05$, 6 hr. DA 5.0 μg: $F(2,10)=9.90$, $p<0.005$, 2 hr; $F(2,10)=27.48$, $p<0.001$, 3 hr; $F(2,10)=41.01$, $p<0.001$, 4 hr; $F(2,10)=40.94$, $p<0.001$, 5 hr; $F(2,10)=76.43$, $p<0.001$, 6 hr; $F(2,10)=36.25$, $p<0.001$, 7 hr; $F(2,10)=7.44$, $p<0.025$, 8 hr. DA 20 μg: $F(2,8)=12.09$, $p<0.005$, 3 hr; $F(2,8)=17.81$, $p<0.005$, 4 hr; $F(2,8)=5.68$, $p<0.05$, 5 hr; $F(2,8)=7.94$, $p<0.025$, 6 hr; $F(2,8)=8.26$, $p<0.025$, 7 hr. DA 40 μg: $F(2,11)=4.71$, $p<0.05$, 5 hr; $F(2,11)=5.14$, $p<0.05$, 6 hr; $F(2,11)=4.74$, $p<0.05$, 7 hr. Student Newman-Keul's test: $*p<0.05$ when compared to young and mature rats; $**p<0.05$ when compared to mature rats; $***p<0.05$ when compared to young rats.

stimulate the locomotor activity of aged rats but the response was reduced and of relatively short duration. Although these results are consistent with a decrease in dopamine receptor function in aged rats, the locomotor activity response of old rats to a dopamine agonist (ergometrine), dopamine alone, or dopamine after pargyline pretreatment do not support this conclusion.

In order to determine whether the decreased response of old rats to dopamine is related to the pretreatment with a monoamine oxidase inhibitor, we examined the response to dopamine of old and mature rats that were not pretreated with a monoamine oxidase inhibitor. Under these conditions, dopamine produced a brief stimulation of locomotor activity, lasting approximately one hour. This decrease in the duration of the response compared to that of rats pretreated with a monoamine oxidase inhibitor is consistent with the concept that dopamine, after intraaccumbens injection, is rapidly metabolized by monoamine oxidase. In contrast to the effects of dopamine in nialamide pretreated rats, it was found that the hypermotility response to dopamine of old rats was not smaller than that of mature rats. In fact, there was a trend toward a greater response in the old rats compared to the mature rats. It has been reported that after injection of dopamine into rat striatum, the dopamine diffused to a greater extent in young compared to old animals [2]. Since the response of old animals is not decreased in the absence of nialamide (Table 1), it is unlikely that the attenuated response of old animals in the presence of

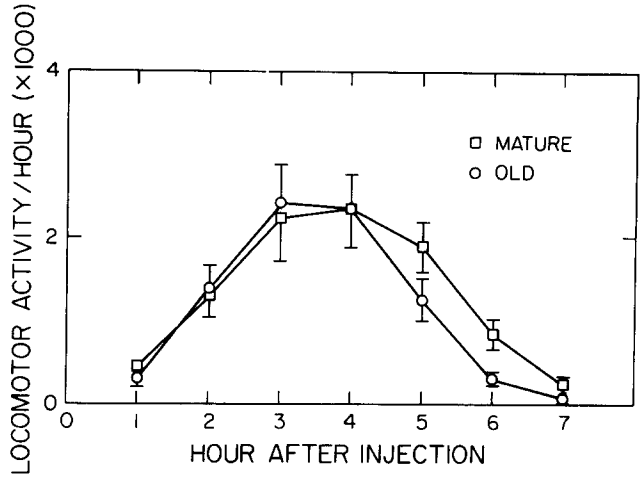

FIG. 4. Effect of intraaccumbens injections of ergometrine (1 μg/0.5 μl) on the locomotor activity of mature and old rats. Locomotor activity was recorded at one hour intervals for 7 hours after the injection of ergometrine. Each point represents the mean one hour activity±S.E.M. of 4–6 rats.

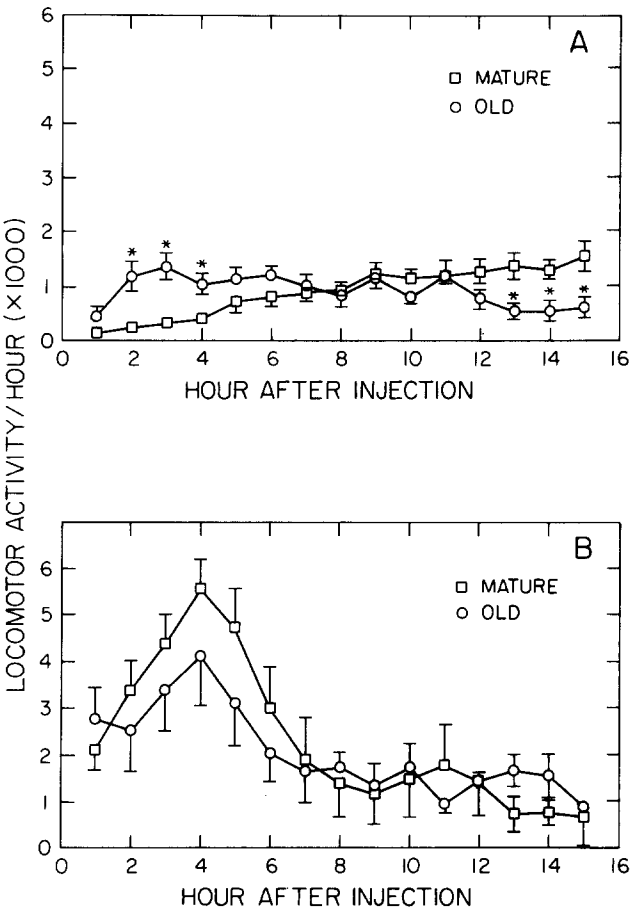

FIG. 5. Time course of the locomotor activity response of pargyline pretreated mature and old rats to intraaccumbens injections of dopamine. Rats were pretreated with pargyline, 75 mg/kg IP, 1.5 hours prior to bilateral intraaccumbens injections of dopamine (20 μg/0.5 μl) or vehicle (0.5 μl). Locomotor activity was recorded at one hour intervals for 15 hours after the injection of dopamine. Baseline activity (pargyline + vehicle, Fig. 5A) was subtracted from activity recorded after the injection of dopamine to get the locomotor activity response/hour (Fig. 5B). Each value represents the mean one hour activity of 3–4 rats±S.E.M. *Activity significantly different from that of mature rats, $p<0.05$.

nialamide is related to diffusion differences. Our results suggest that the reduction in the response to dopamine in old rats pretreated with nialamide is related to the presence of the monoamine oxidase inhibitor.

This hypothesis is supported by our observation that ergometrine, a dopamine agonist that is not metabolized by monoamine oxidase, produced a similar intensity and duration of locomotor activity stimulation in old and mature rats. In addition, although the response of old rats to dopamine was reduced after nialamide pretreatment, it was not significantly decreased if the animals were treated with an alternative monoamine oxidase inhibitor, pargyline. This latter observation suggests that the reduced response of the old rats to dopamine is specific for nialamide and is not a general effect common to all monoamine oxidase inhibitors.

One explanation for the reduced response of nialamide pretreated old rats to dopamine would be that nialamide is unable to inhibit monoamine oxidase in the nucleus accumbens of old rats. Consequently, dopamine, after intraaccumbens injection, would be rapidly metabolized and would not accumulate in the vicinity of postsynaptic dopaminergic receptors. To test this hypothesis, old and mature rats were injected systemically with either saline, nialamide, or pargyline and 5 hours later, monoamine oxidase activity in the nucleus accumbens was determined in-vitro using dopamine as a substrate. It was found that both pargyline and nialamide completely inhibited monoamine oxidase activity in the nucleus accumbens of both mature and old rats. Therefore, the reduced response to dopamine of old rats pretreated with nialamide does not appear to be due to the inability of nialamide to inhibit monoamine oxidase activity. Alternatively, it is possible that the effect of nialamide on monoamine oxidase activity in-vitro does not reflect the effects of the drug on the activity of monoamine oxidase activity in-vivo. Thus, there could be a small pool of monoamine oxidase in the nucleus accumbens of old rats which is not inhibited by nialamide, but which is important in metabolizing injected dopamine. This enzyme pool may be too small to be measured in a homogenate or may be dispersed during homogenization, rendering it susceptible to inhibition by nialamide remaining in the nucleus accumbens after systemic administration. Further studies on the metabolism of dopamine in vivo are needed to assess this possibility.

In summary, these studies show that after nialamide pretreatment, the response to the intraaccumbens administration of dopamine of old rats is markedly reduced compared to that of young and mature rats. The decreased response of old rats does not appear to be due to a decrease in dopamine receptor activity in the nucleus accumbens, to an inability of nialamide to inhibit monoamine oxidase in the nucleus accumbens, or to a physical impairment in old rats which prevents them from responding to dopamine with high rates of locomotor activity. Instead, the decreased response appears

to be related to a selective effect of nialamide in old rats that does not occur in either young or mature rats. The nature of this unique action of nialamide in old rats is at present unclear, but it results in an attenuated response to the intraaccumbens injection of dopamine.

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