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Individual Motor Activity—Relationships to Dopaminergic Responses

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SCHUMACHER, H. E., J. OEHLER AND M. JAEHKEL. *Individual motor activity—Relationships to dopaminergic responses.* PHARMACOL BIOCHEM BEHAV **48**(4) 839–844, 1994.—Owing to motor activity mice were divided into two groups in a running-wheel test: low-active mice (LAM) and high-active mice (HAM). Locomotor activities in the running wheel and in glass boxes are compared. The HAM showed a more intensive explorative behavior than LAM and were also more responsive in terms of exogenous factors than LAM. In contrast, LAM showed higher locomotor activity than HAM after habituation. Analyzing the response of LAM and HAM to dopaminergic agonists such as apomorphine, bromocriptine, and amphetamine, the role of specific dopaminergic mechanisms for the two types is discussed. Although apomorphine mainly stimulated the climbing activity in HAM, bromocriptine (climbing activity) and amphetamine (locomotion) had stronger effects in LAM. Differences may be assumed between LAM and HAM concerning the nigrostriatal and/or mesolimbic dopaminergic mechanisms. On the one hand, climbing activity following apomorphine application accompanied by stereotypes may suggest a stronger activation of striatal dopaminergic mechanisms in HAM. On the other hand, climbing activity following bromocriptine accompanied by jumping behavior, as well as the stimulation of locomotion after amphetamine, suggests a more effective activation of mesolimbic dopaminergic structures in LAM.

Individual behavior Running wheel Locomotion Exploration Habituation Dopaminergic agonists Apomorphine Amphetamine Bromocriptine

THERE are considerable interindividual differences in activity level regarding motor behavior in experimentally used animals. Investigation of running-wheel activity in mice shows that some animals cover several hundred metres a night, whereas others do several kilometres (35).

The dopaminergic transmission system is supposed to play an essential role in generating motor behavior such as locomotion (4,13) and climbing (8,31). It may be assumed that individual specific functions of dopaminergic mechanisms are important neurobiological causes for triggering individual motor activities. Investigations of mouse strains show that mice presenting higher locomotor activity in the open field are provided with more dopaminergic neurons in the substantia nigra and more [^{3}H]spiroperidol binding sites in the striatum (15,32). Correlations between motor activity levels, strain-specific dopaminergic functions, and specific responses to dopaminergic agonists and antagonists, respectively, are evident (12,15,32). Furthermore, strain-specific distribution of dopaminergic receptors in the nucleus accumbens or substantia nigra is essential for different behavioral responses after high doses of apomorphine or amphetamine (34). Spirduso et al. (36) demonstrated in rats that animals, belonging to one strain and different in their motor activity level, also have specific numbers of [^{3}H]spiroperidol binding sites and show specific reactions to dopaminergic agonists. Different responses to neuroleptics were also established in rats that had been related to extreme types according to response to the dopaminergic agonist (−)*N*-*n*-propyl-norapomorphine (7).

Because modified dopaminergic transmission processes are thought to be of potentially pathogenetic importance with respect to psychoses such as schizophrenia (16,17) and because there is considerable individual variety in the response to neuroleptics, experimental animal studies concerning relationships between individual motor activity, neurobiological disposition, and pharmacological effects are of clinical relevance. This is particularly interesting for investigations on animals of one strain that had been selected according to their motor phenotype.

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Here the direct relation between activity level of dopaminergic transmission processes and motor activity is of essential importance for selecting animals according to their spontaneous behavior. Central dopaminergic structures are involved to a different degree in generating various motor parameters. Therefore, the method used for differentiating behavioral types may be important for determining certain neurobiological correlations. Whereas the nucleus accumbens is assumed to play an important role in generating locomotor behavior, climbing behavior may be influenced by different mesolimbic and striatal structures (8,31). Little is known about any involvement of dopaminergic structures in generating running-wheel behavior (25). Owing to considerable interindividual difference, which are reproducible, this mode of behavior appears to be of particular interest and may serve as a basis for neurobiological characterization (25,35).

In the present study we investigate if mice of one strain, which were selected according to their running-wheel activity as low-active mice (LAM) and high-active mice (HAM), differ in specific dopaminergic mechanisms. First we analyze if relationships can be found between the activity determined in the running wheel and the spontaneous locomotor activity in a motilimeter. Then the responses to apomorphine, bromocriptine, and amphetamine are studied. Therefore, different functions of synaptic transmission in low-active mice and high-active mice are characterized by means of dopaminergic substances that trigger their agonistic effect via different mechanisms.

METHOD

Animals

We used 4- to 5-week-old male mice of the strain AB/Jena (Co. Hirsch, Heidenau, Germany), weighing 18–24 g. The animals were provided with standard food and drinking water ad lib. They were kept in a conventional manner at a 12 L : 12 D regime. We used random samples, consisting of 10 animals, kept in standards cages (55 × 40 × 10 cm) for 1 week. Thereafter, determination of running-wheel activity and type classification was started.

Running-Wheel Activity and Selection Criteria

The investigation was based on establishing individual running-wheel activity. Running-wheel activity per 1 h was determined between 0700 and 1200 h 6–10 days following group formation. For that reason, the mice were put in running-wheel equipment containing 10 separate wheels.

The animals' activity was determined quantitatively by means of sensors attached to the running wheel. A total rotation resulted in four pulses to be measured; even slight movements of the running wheel could be detected. The pulses were registered by an electronic counter.

Before the test began, the 10 mice belonging to one group were marked. At the end of the 1-h running-wheel test these two animals out of each group showing the lowest and highest running-wheel activity were labeled. They were then put together into one cage again and remained in their groups until the start of the experiments. There were 3-day intervals between determination of the individual running-wheel activity and the experiments.

At least eight low-active mice (LAM) and eight high-active mice (HAM) out of 40 animals were used in the test series described below. In some cases, the tests were repeated (n = 16 out of 80; n = 32 out of 160). The animals were used only once in a test.

Locomotor Activity

The mice were put individually into glass boxes (35 cm long, 35 cm deep, and 20 cm high), with two parallel horizontal infrared light beams, to determine their locomotor activity. Any interruption of a light beam by the mouse caused a pulse indicated by an electronic counter. The number of interruptions of the light beams was scored every 7.5 min during a 60-min period. Thus, satisfactory disintegration of activity could be obtained. Once the animals had been put into boxes, measurement of locomotor activity started immediately.

Climbing Behavior

After a habituation time of 30 min in the climbing cages made of screen wire (25 cm in height, 12 cm in diameter), the spontaneous climbing of mice was scored. Determination of climbing activity was based on the method described by Protais et al. (31): five times at the beginning of succeeding minutes the behavior of the mice was measured: 0—all paws on the floor; 1—forepaws at the wall; 2—with all paws at the wall. The five values were summarized. After determination of spontaneous climbing, transmitter-specific drugs were administered IP and the climbing behavior was scored again.

Pharmacological Investigations

Apomorphine. The effects of apomorphine were studied by analyzing the climbing activity before and after drug administration via a cumulative dose–response curve. Following the determination of spontaneous climbing, 0.05 mg/kg apomorphine was injected. Ten minutes after this first application the effect was scored. Subsequently, the next doses (0.1, 0.5, 1.0, and 2.0 mg/kg) were administered to the same animal and the climbing was scored after 10 min.

Bromocriptine. The doses of 3 mg/kg bromocriptine were given IP to record the time course of bromocriptine effect by determining the climbing activity in LAM and HAM. The climbing activity was scored 10, 15, 30, 60, 120, 180, and 240 min after drug administration in the same animal. Control animals (LAM and HAM) received equal quantities of 0.9% NaCl solution.

Amphetamine. The effect of 1.0 mg/kg amphetamine was analyzed by determining the locomotor activity in glass boxes. After a 60-min habituation period the drug was administered IP and the effect on locomotion was measured by light beam interruptions between 15 and 30 min after the injection. The control animals received NaCl.

Statistics

Values are presented as mean ± SEM. The means of treated and untreated groups as well as the means of LAM and HAM were compared using the Student's t-test.

RESULTS

Behavioral Investigations

Running-wheel activity. Analysis of the running-wheel activity of both types shows that HAM have higher motor activities than LAM during the observation period (Fig. 1).

Locomotion. The sum of locomotor activity in LAM and HAM measured during the 1-h period does not significantly

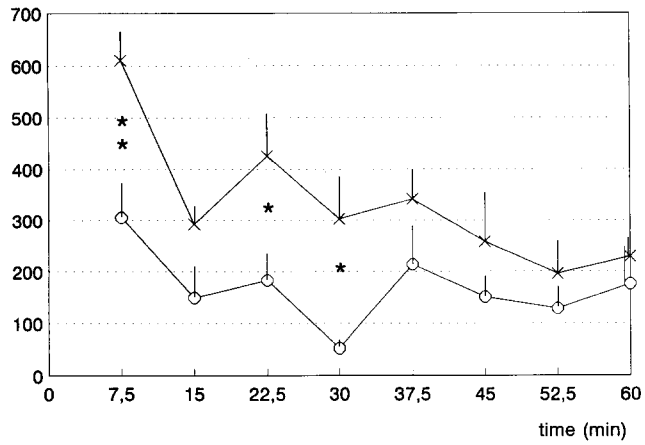

FIG. 1. Time course of running-wheel activity (pulses/7.5 min) in LAM (○, n = 8) and HAM (X, n = 8). Vertical bars represent SEM. *$p < 0.05$, **$p < 0.01$ LAM vs. HAM.

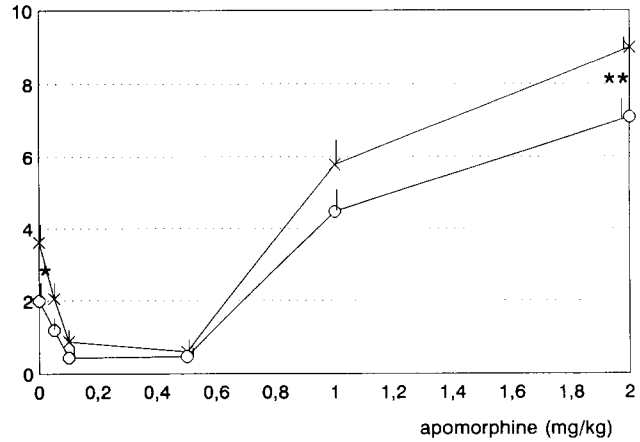

FIG. 3. Dose-response curves of apomorphine on climbing behavior in LAM (○, n = 32) and HAM (X, n = 32). Vertical bars represent SEM. *$p < 0.05$, **$p < 0.01$ LAM vs. HAM.

differ. The number of interruptions of light beams amounted to 622.75 ± 68.00 in LAM and 532.50 ± 58.38 in HAM. But locomotor activity during this hour presented characteristic type-specific variations (Fig. 2). The type-specific difference in activity can be reproduced only within the first 7.5 min (exploration phase); 7.5 min later (15 min) the HAM's locomotor activity decreased to a value lower than of LAM. Up to the end of observation, the HAM's activity continued to decrease steadily but not intensively. In general, the LAM's decrease in activity was less than in HAM. After about 15 min, mice that were low-active in the running wheel revealed even higher locomotion than the HAM.

Pharmacological Investigations

Apomorphine. The cumulative apomorphine dose-response curve revealed type-specific differences (Fig. 3). Having started with significantly ($p < 0.05$) different levels of spontaneous climbing behavior, both types demonstrated the lowest climbing activity at 0.5 mg/kg. But the inhibitory influence of 0.05 mg/kg apomorphine on the spontaneous climbing activity was significant only in HAM ($p < 0.05$). After the inhibitory apomorphine doses, stimulation of the climbing activity increased after 1.0 mg/kg apomorphine and increased again at 2.0 mg/kg ($p < 0.01$).

Bromocriptine. The time course of bromocriptine effect demonstrated type-specific differences. In HAM a significant decrease of the climbing activity was noted 10 min following the administration of 3.0 mg/kg bromocriptine. By the end of the experiment (240 min), the activity values were also lower in HAM than in those of the control animals. The LAM decreased activity only immediately after bromocriptine administration. After the 60th min, stimulating effects of bromocriptine were observed in LAM. They were significant at 3 h postadministration (Fig. 4a,b).

Amphetamine. The stimulating effect of amphetamine (1.0 mg/kg) on the locomotor activity measured in glass boxes was different in LAM and HAM. The LAM responded with a significant increase of locomotion in comparison to control animals of the same activity type (Table 1). In HAM only a small amphetamine-induced increase of locomotor activity was seen.

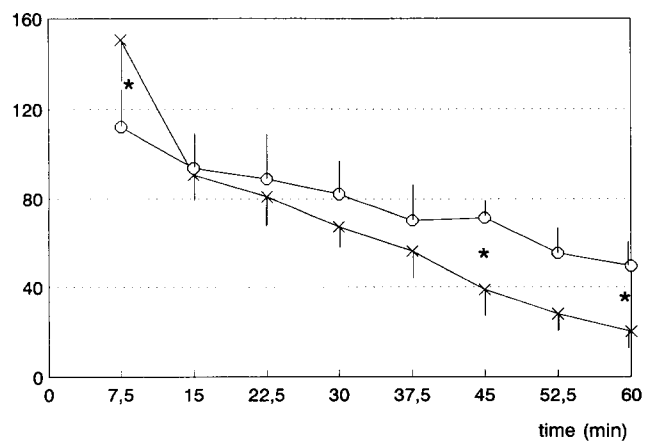

FIG. 2. Time course of locomotor activity (interruptions of light beams/7.5 min) in LAM (○, n = 8) and HAM (X, n = 8). Vertical bars represent SEM. *$p < 0.05$ LAM vs. HAM.

DISCUSSION

Activity of mice in the running wheel varies interindividually. HAM can achieve values four to five times as high as LAM measured within 1 h. According to Silverman (35), feedback mechanisms are likely to be involved in running-wheel behavior. The activity mechanisms playing a part may be described as: the animal's effort to move the wheel leads to some impairments of equilibrium and can only be reestablished by further movement. Those tactile, acoustic, and optical stimuli related to rotation present a permanent exogenous drive.

According to File (11), behavioral intensity and duration in an explorative situation are influenced by the animal's internal status, that is, food motivation, hormonal status, and by the new environment (e.g., complexity, novelty). Thus, exogenous sensoric stimuli promote explorative behavior (10,24,28,37).

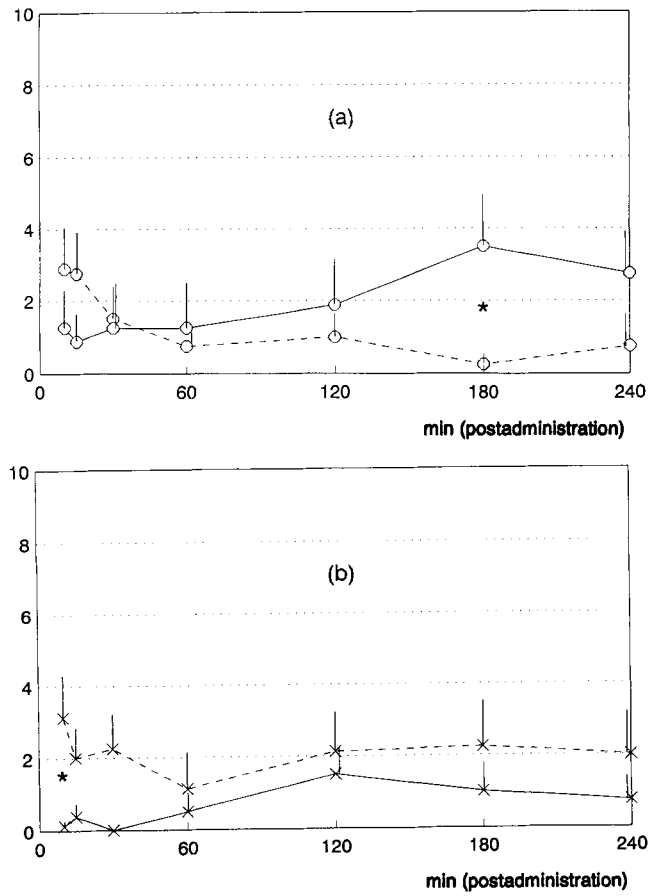

FIG. 4. Influence of 3.0 mg/kg bromocriptine (time course) on climbing behavior in (a) LAM (○, $n = 8$) and (b) HAM (X, $n = 8$). *$p < 0.05$ vs. control groups LAM and HAM, respectively. Vertical bars represent SEM.

Locomotor activity during exploration is, among others, connected with the function of mesolimbic dopaminergic structures (14). Some authors (19,21) suggest that motor activities are also influenced by the striatal dopaminergic system when there is an unfamiliar environment, and therefore exogenous stimuli induce "sensomotor arousal" (19).

In rats, one-sided intrastriatal dopamine application leads to increased orientation reactions compared to sensoric stimuli (21). On the other hand, one-sided 6-OHDA lesion of the substantia nigra prevents any corresponding motor reaction. Hence, it is believed that the nigrostriatal tract is not simply involved in generating motor behavior but plays an essential role in sensomotor integration (38). A relationship between the level of running-wheel activity and response to sensoric stimuli is demonstrated in investigations by Bert et al. (1). Using two mouse strains they were able to show the existence of strain-specific differences in running-wheel activity and direct relations to quantitative differences in somatosensoric orientation response. This was associated with differences in sensitivity of striatal dopaminergic receptors to dopaminergic agonists. Based on these findings, the question arises whether the motor activity established in our LAM and HAM manifests specific features of the nigrostriatal dopaminergic system.

TABLE 1

EFFECT OF AMPHETAMINE ON LOCOMOTOR ACTIVITY

Type	Control	Amphetamine	Significance
LAM	59.12 ± 13.61	347.38 ± 52.25	$p < 0.01$
HAM	150.88 ± 49.50	321.50 ± 76.96	NS

Values are mean ± SEM of the number of interruptions of light beams during 30 min. $n = 8$.

The HAM's and LAM's locomotor activities measured for 1 h in the motilimeter present a different course. The decrease in locomotor activity, probably due to habituation processes, is more rapid in HAM. Type-specific differences in activity decrease result in higher locomotor values displayed by initially less active mice after 15 min. In comparison to more exogenously influenced locomotor activity during exploration in an unfamiliar environment, the locomotion after habituation seems to reflect the endogenous activity state. According to Iversen (19), this activity seems to be an expression of a "motivational arousal" and might be associated with the mesolimbic system. Therefore, higher activity values in LAM after habituation may be caused by type-specific mesolimbic activity. Our further studies using different dopaminergic agonists show type-specific reactions that may actually be attributed to specific dopaminergic dispositions in LAM and HAM.

Apomorphine administered in high doses leads to stimulation of climbing activity by affecting the postsynaptic dopaminergic receptors (2). In our experiments, this effect has been found to be stronger in high-active mice than in low-active mice. Pharmacokinetic differences do not play a role due to parallel time course of apomorphine effects after 5.0 mg/kg (results not shown). Based on investigations of different mouse strains, positive correlations are known to exist between locomotor activity level, number of dopaminergic neurons, and response to apomorphine and amphetamine (12,15, 26,32). Because climbing activity—according to Costall et al. (5,7)—can be stimulated by pharmacological activation of different dopaminergic systems, the question whether there is a neurobiological background cannot clearly be answered at present. Some authors emphasize a special impact of striatal dopaminergic structures for generating climbing activity with this being a clue for differences in striatal mechanisms (30).

In our experiments, behavior of LAM and HAM in the climbing cages after administration of 2.0 mg/kg apomorphine is mainly characterized not only by climbing activity but also by stereotypes such as licking, gnawing, and sniffing. However, the method used does not provide any quantitative or qualitative differentiation of climbing activities in the sense of general body movements or stereotypes. More precise observations show that after administering higher doses of apomorphine, stereotypes appear in phases of relative rest in which mice hold themselves with all four paws at the walls of the climbing cage. Because this behavior is scored with two points and the HAM show higher values in their climbing activity than LAM, the conclusion can be drawn that HAM develop stereotypes faster than LAM following an increase of apomorphine doses. Suppression of total body movements—as happens during locomotion by appearance of stereotypes—is a well-known phenomenon (18). In general, striatal dopaminergic structures are supposed to play an essential role for

triggering stereotypes such as licking, gnawing, or biting (2). In mouse strains with less [^{3}H]spiroperidol binding sites in the striatum, an increase of locomotor activity up to a constant high level was registered after apomorphine doses had been raised. Mice with a higher number of such binding sites responded to increased apomorphine doses with a considerable development of stereotypes and at the same time a decrease of locomotor activity (27,40). Thus, it is not unlikely that similar relationships matter for our types too; i.e., the higher values in climbing activity registered in HAM after higher apomorphine doses may be explained by stronger activation of striatal dopaminergic mechanisms.

Contrary to apomorphine-stimulated climbing behavior, the climbing induced by bromocriptine was mainly characterized by active, total body movements and frequent jumping against the climbing cages, and stereotypes could not be established. Hence, stimulated climbing following the application of bromocriptine could be clearly differentiated in a qualitative way from climbing subsequent to stimulating doses of apomorphine. Climbing activity stimulated by bromocriptine is thought to be due to stimulating mesolimbic dopaminergic structures (20). Hence, for generating jumping behavior considerable importance is assigned to the tuberculum olfactorium (39).

In comparison to HAM, the LAM showing stimulated climbing activity after bromocriptine are supposed to have higher efficiency of the mesolimbic dopaminergic system. This is supported by the fact that amphetamine leads to a significant stimulation of locomotor activity only in the LAM, with this behavioral effect being a result of activation of mesolimbic dopaminergic structures (2,4,9,23,29).

A different number of dopaminergic receptors in the dopaminergic structures of LAM and HAM may cause different effects of amphetamine in both types. So the pharmacological effect of a certain dose of amphetamine on the behavior seems to be the result of activating mesolimbic and striatal dopaminergic structures (33). Whereas a higher number of postsynaptic receptors in the nucleus accumbens is favourable to the stimulating effect of amphetamine on locomotion (32), a higher number of striatal dopaminergic receptors probably has an antagonistic effect (22).

In conclusion, these results show that different motor phenotypes of a mouse strain may be influenced by type-specific mechanisms of the mesolimbic and/or striatal dopaminergic transmission system. Whether these specific mechanisms directly depend on structural type-specific characteristics such as the number of dopaminergic terminals or the number of receptors remains as a subject of further investigations.

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