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Influence of Nootropic and Antidepressive Drugs on Open Field and Running Wheel Behavior in Spontaneously High and Low Active Mice

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JÄHKEL, M., J. OEHLER AND H.-E. SCHUMACHER. *Influence of nootropic and antidepressive drugs on open field and running wheel behavior in spontaneously high and low active mice.* PHARMACOL BIOCHEM BEHAV **49**(2) 263–269, 1994. – Mice differentiated by their running wheel activity into low and high active animals were chronically treated with the nootropics meclophenoxate, piracetam, vinpocetine, methylglucaminorotate, and the antidepressants lithium, desipramine, amitriptyline, and clomipramine. The influence of chronic drug treatment on running-wheel activity and open field locomotor behaviour was analyzed. Whereas with antidepressants rather sedative effects were observed in both activity types, the effects of nootropics were different in high and low active mice. Running-wheel scores increased in low active mice but decreased in high-active animals with an improvement in efficiency of locomotor behaviour in the open field of these mice after chronic nootropic treatment. In general, the effects of antidepressants seemed to be more uniform than those of the nootropics used.

Mice Behavioural activity types Nootropics Antidepressants Long-term treatment Running-wheel Open field

AS EARLY as in the 1970s, nootropics were investigated as psychotropic drugs, predominantly improving learning and memory processes, transcallosal interhemispheric information transfer as well as cortical and subcortical control functions (4,5,10,21,22). Furthermore, they increase the resistance of brain cells to hypoxia and intoxication (8,22). Some biochemical, electrophysiological, and pharmacological data suggest an involvement of monoaminergic and cholinergic transmission processes in response mechanisms of nootropics (3,6,11,13,16, 17,20).

Experimental findings regarding nootropic induced behavioural alterations are contradictory. This may be due to insufficient doses or irrelevant behavioural tests. Long-term applications of nootropic drugs are certainly necessary for developing behavioural effects. On the other hand, individually different dispositions and state-dependent conditions might be significant for the response profile of nootropics.

We tried to consider these aspects in the investigations presented, and analyzed the effects of long-term nootropic treatment on running wheel and open field behaviour in mice characterized by spontaneously high and low activity in a previous running wheel test. Investigations in our lab hint on specific dopaminergic sensitivities of these two mice types and also on different stress resistance supposing similarities to human differences in cerebral disease disposition (7,14).

In comparison, therapeutically well-described antidepressants are used because of their drive and mood improving properties.

METHOD

Subjects

Male mice (strain AB, Hirsch Heidenau) were used. At the beginning of our investigations the animals were 4–6 weeks

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old. They were kept in standard cages in groups of ten mice in a 12/12 hour light/dark regime with food and water ad lib. Initially, ten animals were subjected to a one hour running wheel test. Those two animals showing the highest and lowest activity were put in new groups comprising ten high (HAM) and ten low active mice (LAM).

All animals were used only once as controls or for one drug treatment with the subsequent behavioural tests. Ten HAM and ten LAM as controls and treated animals were used for one test trial.

Control groups of HAM and LAM received pure drinking water. The water consumption of our mice was about 175 ml/kg per day. Therefore, the daily drug doses were dissolved in 175 ml drinking water per 1 kg mice of the test groups. The pretreatment period took two weeks and was continued in the weeks of the test period. The following substances and doses were applied: piracetam 200 mg/kg (pir), meclophenoxate 200 mg/kg (cer), methylglucamineorotate 225 mg/kg (mgo), vinpocetine 10 mg/kg (vin), desipramine 5 mg/kg (des), amitriptyline 5 mg/kg (ami), clomipramine 5 mg/kg (clo) and lithium 4 nmol/kg (li).

Apparatus

Running wheels. In all tests we used a running wheel apparatus, where ten wheels are placed side by side. The wheels were 13.5 cm in diameter and 4-cm wide with brass rungs every 2.5 cm between the plastic sides. Mice were introduced through a 4.5 cm hole on one side of the wheel. On the other side four magnets were arranged every 90° to record even slight movements of the wheel. When the wheels hung in the apparatus mice could not leave their wheel.

Open Field

The open field arena was a plastic arena of 60 cm × 40 cm with a 20 cm high wall. The arena was provided with a transparent lid. A usual 40 Watt lamp was installed 1.5 m above the arena. On the long sides of the wall were 8 and on the small sides were 4 infrared light beams "dividing" the arena in 32 equal rectangles—"squares" at a distance 1 cm above the floor. Every 1 s the place and the way of the mice were determined optoelectronically by the light beam interruptions.

Procedures

Experiments were started at the third week of drug treatments. The animals' activity was measured on 10 subsequent days in a 1-h running wheel test. Impulses of running wheel movements were recorded electromagnetically. Activity increase induced by these repeated sessions was determined and compared in control and treated animals using the activity values of the first and the last activity measurement of each mouse for paired Student's *t*-test evaluation.

On the last day, at which time the treatment was carried out for the fourth week, locomotor activity of the same animals was analyzed in an open field test. During 10 minutes the movements of the mice were recorded optoelectronically. The

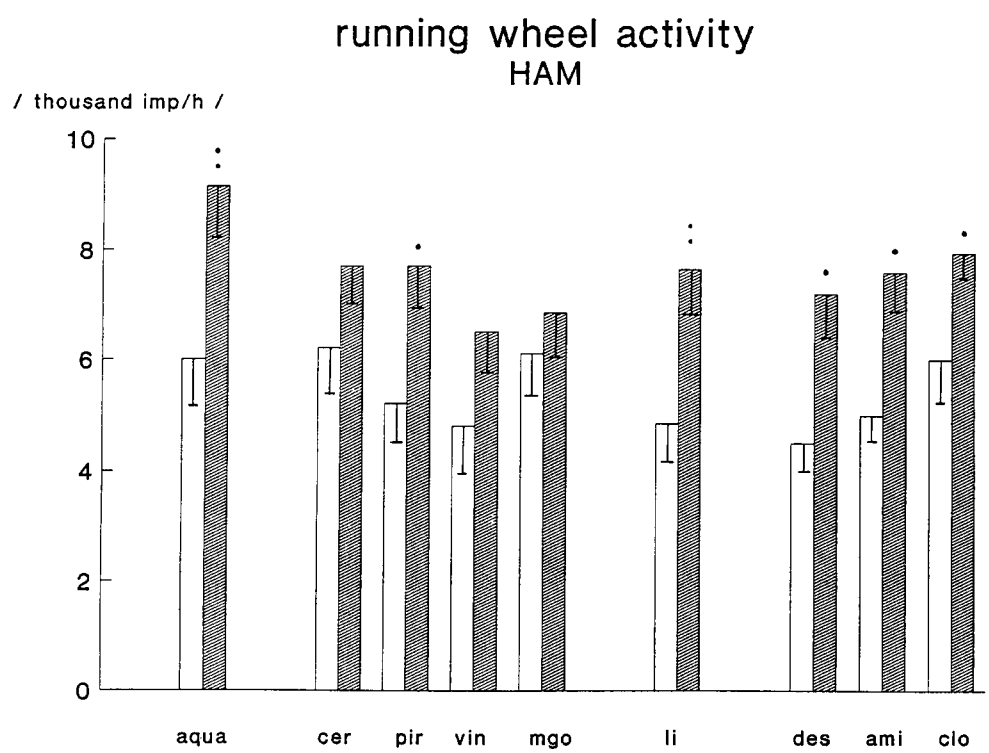

FIG. 1. Activity increase induced by repeated 1 h running wheel session in comparison to running wheel activity during the first test trial of chronically pretreated high active mice (HAM) receiving pure drinking water (aqua) or the following substances: meclophenoxate (cer), piracetam (pir), vinpocetine (vin), methylclucamineorotat (mgo), lithium (li), desipramine (des), amitriptyline (ami), clomopramine (clo). Mean ± SEM; $*p < 0.05$ $**p < 0.001$).

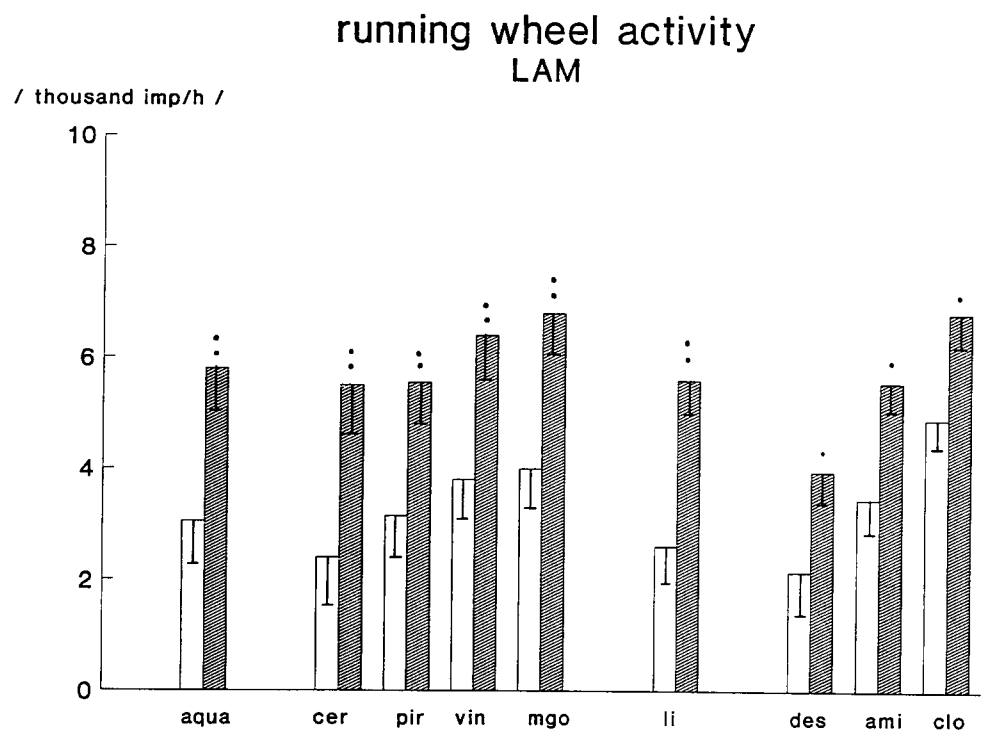

FIG. 2. Activity increase induced by repeated 1 h running wheel sessions in comparison to running wheel activity during the first test trial of chronically pretreated low active mice receiving pure drinking water (aqua) or the following substances: meclophenoxate (cer), piracetam (pir), vinpocetine (vin), methylclucamineorotat (mgo), lithium (li), desipramine (des), amitriptyline (ami), clomopramine (clo). Mean ± SEM; $*p < 0.05$ $**p < 0.001$.

following parameters were measured: (a) squares crossed in total; (b) border squares; (c) middle squares; (d) quotient 2./3.; (e) time spent on the border; (f) time spent in the middle; (g) quotient 5./6.; (h) frequency at the first place—it means the highest frequency of visiting any one of the squares; (i) time at the first place—it means preferred place; (j) quotient frequency of the 15th place to frequency of the first place; (k) mean of squares crossed every 40 seconds; (l) active time—sum of seconds crossing at least one square; (m) passive time—sum of seconds spend longer than 1 second on one square; (n) number of passive phases lasting longer than 10 seconds; (o) active phases on the border > 4 s; (p) active phases on the border < 4 s; (q) active phases in the middle > 4 s; and (r) active phases in the middle < 4 sec.

As has been shown in a previous factor analysis, these 18 parameters revealed three independent factors. In accordance to the events loaded the factors were named: factor 1 "activity"; factor 2 "place utilization"; factor 3 "place preference" (15). The Student's *t*-test was used for comparison of place utilization in treated or untreated mice. Statistics were made only between mice of one test trial. In the schemes controls were summarized.

RESULTS

Running Wheel Activity

The test sessions repeatedly performed induced a significant increase ($p < 0.01$) in running wheel activity of control mice, with this being independent on the previously determined activity state of the HAM and LAM (Figs. 1 and 2). Chronic drug pretreatment induced type- and substance-specific alterations of running wheel activity. In HAM the nootropics, except for piracetam (pir) ($p < 0,01$), prevented a significant increase of running wheel activity during repeated test sessions (Fig. 1). In LAM, the increase of running wheel activity ($p < 0.01$) was seen in mice receiving the nootropics (Fig. 2).

Long-term application of lithium (li) seemed to have no effects on the increase of running wheel activity in HAM and LAM. The antidepressive drugs rather attenuated the running wheel activity increase ($p < 0.05$ in comparison to $p < 0.01$ of controls) in both mice types. The effect of desipramine (des) was distinct, considering also the low activities before repeated running wheel sessions.

Open Field Locomotion

When analyzing the number of squares crossed during 10 minutes, significant effects of chronic drug administration were not detected in any case. Besides the activity of HAM and LAM is nearly the same (Figs. 3, 4). Factor 1 "activity," received by factor analysis of the 18 measured parameters, reflected the same and was not shown.

Factor 2 "place utilization" as an integrating quantitative value of all parameters determined permit assessment of the explorative quality in mice behaviour. The results regarding factor 2 demonstrated obvious type-specific drug effects, especially following meclophenoxate (cer) and vinpocetine (vin)

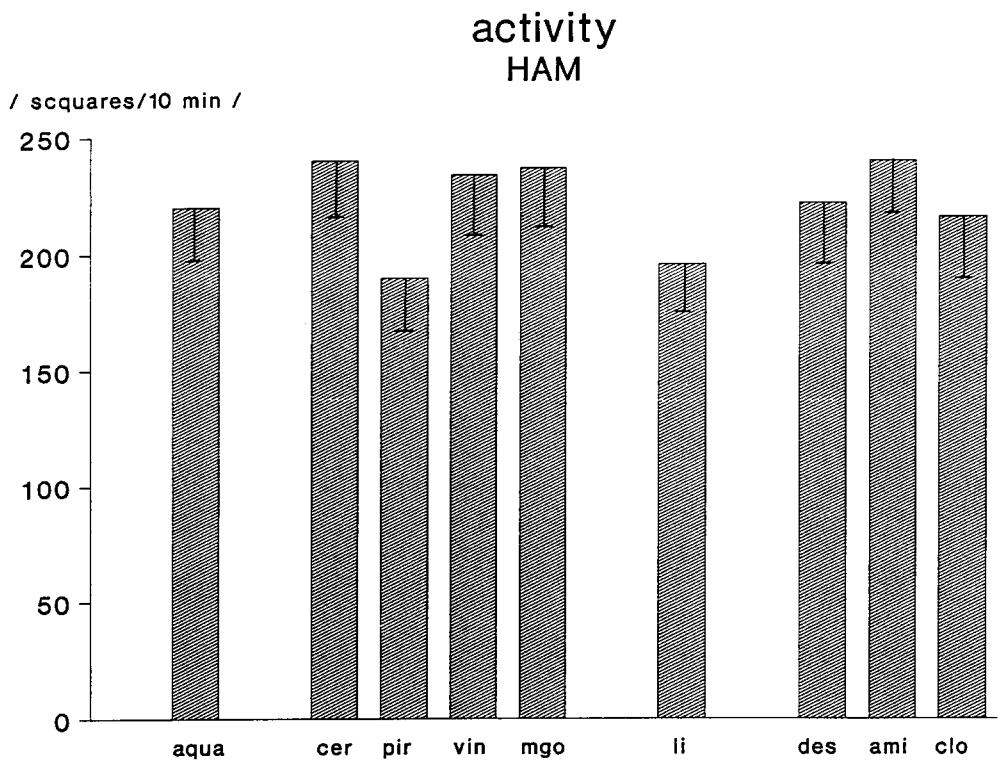

FIG. 3. Open field activity of high active mice (HAM) receiving pure drinking water (aqua) or the following substances during a 4-week pretreatment period: meclophenoxate (cer), piracetam (pir), vinpocetine (vin), methylclucamineorotat (mgo), lithium (li), desipramine (des), amitriptyline (ami), clomopramine (clo). Mean ± SEM.

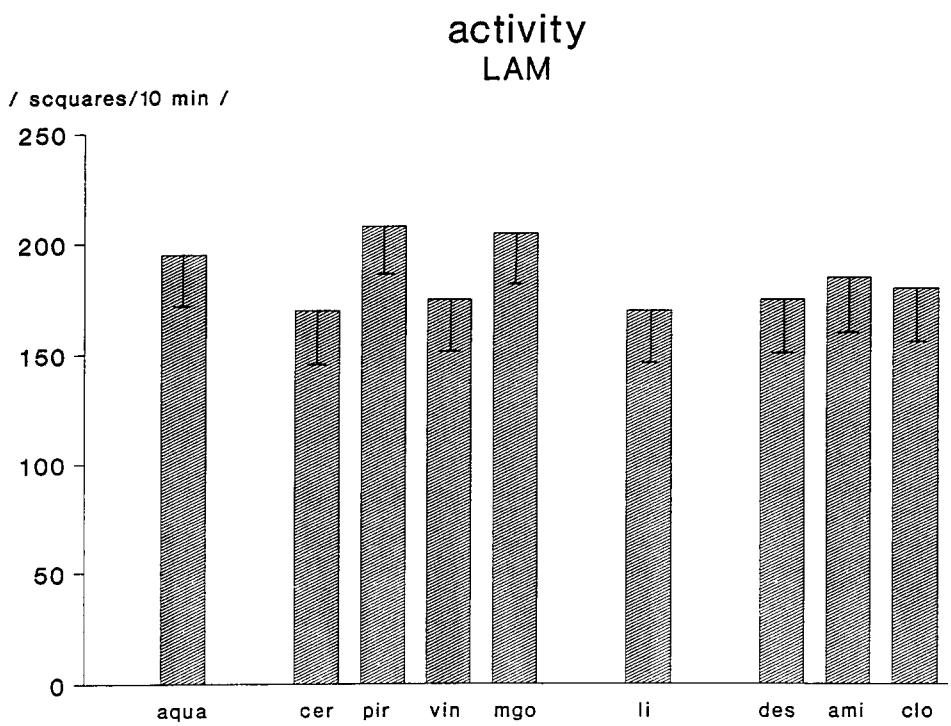

FIG. 4. Open field activity of low active mice (LAM) receiving pure drinking water (aqua) or the following substances during a 4-week pretreatment period: meclophenoxate (cer), piracetam (pir), vinpocetine (vin), methylclucamineorotat (mgo), lithium (li), desipramine (des), amitriptyline (ami), clomopramine (clo). Mean ± SEM.

(Figs. 5, 6). Meclophenoxate (cer) induced an improvement of "place utilization" in HAM. In LAM a decrease of factor 2 was seen. Similar effects were observed after vin in comparison to untreated type-specific controls. An improvement of "place utilization" in HAM was also demonstrated after methylglucamineorotate (mgo), whereas the same substance was ineffective in LAM. Significant alterations of the factor 2 were not detectable in HAM and LAM after pir had been applied.

The antidepressive drugs desipramine (des) and amitriptyline (ami) caused a decrease of factor 2 "place utilization," especially in LAM. On the other hand pretreatment with clomipramine (clo) seemed to have no influences on factor 2. After lithium (li), an increase in factor 2 could be demonstrated in HAM.

Factor 3 "place preference" is a value for locomotions related to a favourite place or to stereotyped running. In the experiments described factor 3 was in an inverse relation to factor 2 and not separately shown.

DISCUSSION

Different and widespread behavioural analyses are necessary to receive a sufficient concept of the response profile of drugs with "nootropic" qualities. On the one hand, considering the clinical implications a differentiation is necessary (5). On the other hand, analysis of dose response relationships under long-term applications needs further interest.

Improvement of mental and psychophysical fitness is one of the target objectives for using psychotropic drugs (2,10,17). Interindividual differences in drug efficacy are obvious. We especially tried to consider such type-specific distinctions by using mice types different in their behaviour.

First we could not find any clear stimulation of the locomotor activity. Thus this parameter confirms previous investigations (1,12,19). On the other hand, we were able to demonstrate nootropic influence on qualitative locomotor events. These concerned the increasing locomotor activity after repeated test sessions in the running wheel as well as changes of place utilization during explorative behaviour in an open field determined by factor analysis of locomotor events.

Type-specific, different effects of nootropics on running wheel activity were obvious. Whereas the increase of running wheel activity in HAM was reduced under nootropic treatment, this increase was partly reinforced in LAM. The very different effects of nootropic drugs demonstrated just on mice of specific functional states indicate that nootropics influence central nervous mechanisms thus going beyond simple stimulation of activity (1,18).

Factor analysis of open field activity underlines this assumption. Considering only the activity measured (squares crossed per time) an influence of nootropic treatment could not be observed. But distinct, especially type-specific, differences were seen after factor analysis of locomotor events considering spatial exploration (F 2 [space utilization]). As for LAM, a deterioration of previous parameter was observed after cer and vin, pir and mgo tended to increase place utilization in LAM and in HAM, respectively.

In general, improvement of place utilization was a remark-

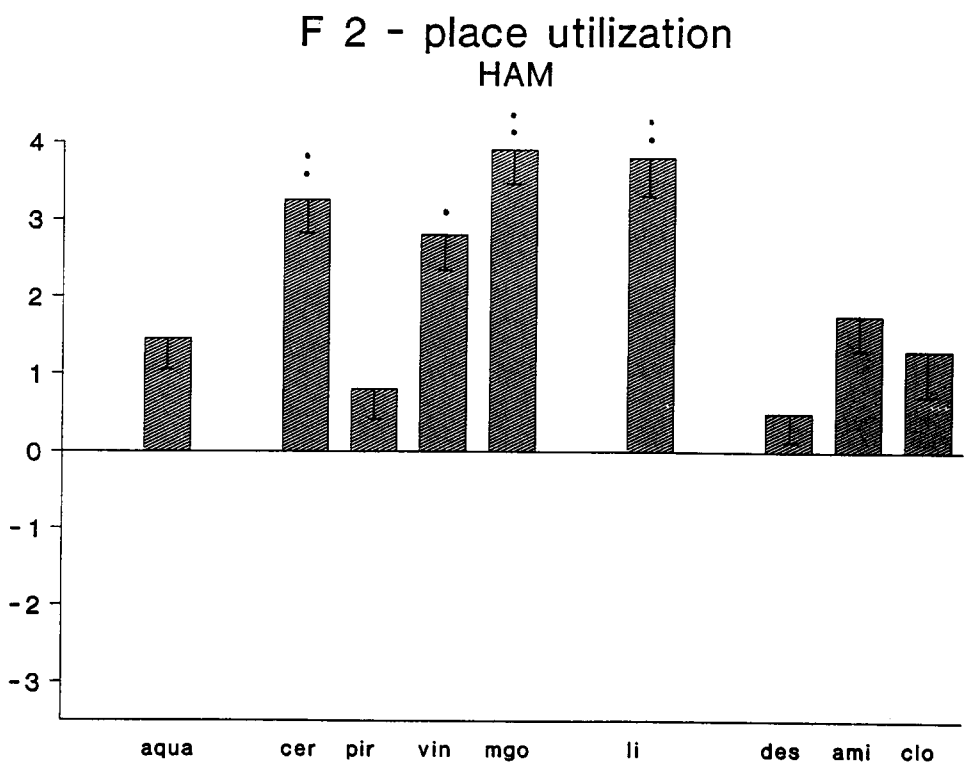

FIG. 5. "F2—place utilization" determined by factor analysis of locomotion parameters measured during a 10-min open field test of high active mice (HAM) receiving pure drinking water (aqua) or the following substances during a 4-week-pretreatment period: meclophenoxate (cer), piracetam (pir), vinpocetine (vin), methylclucamineorotat (mgo), lithium (li), desipramine (des), amitriptyline (ami), clomopramine (clo). Mean ± SEM; $*p < 0.05$; $**p < 0.01$).

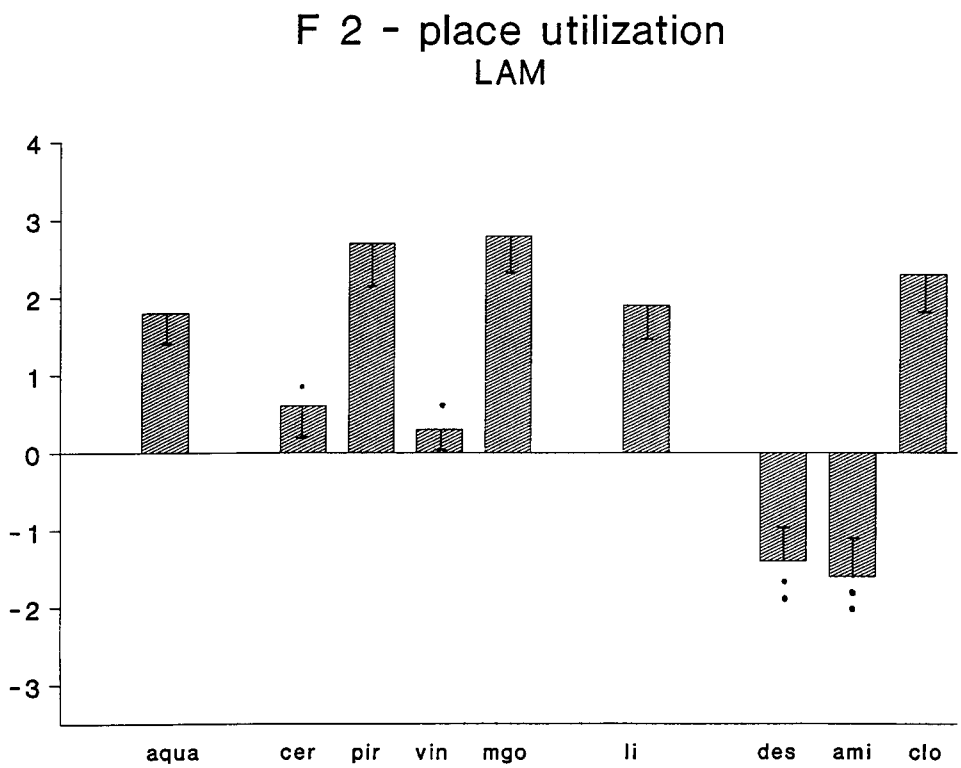

FIG. 6. "F2—place utilization" determined by factor analysis of locomotion parameters measured during a 10-min open field test of low active mice (LAM) receiving pure drinking water (aqua) or the following substances during a 4-week pretreatment period: meclophenoxate (cer), piracetam (pir), vinpocetine (vin), methylclucamineorotat (mgo), lithium (li), desipramine (des), amitriptyline (ami), clomopramine (clo). Mean ± SEM; $*p < 0.05$; $**p < 0.01$).

able effect in HAM induced by the nootropics excluding pir. As HAM also show considerable behavioural responses during exogenous stress situations (7,14), we suppose that the effects of nootropics are dependent on the endogenous state of these mice.

Analysis of clinically well-known antidepressants demonstrate clear differences in comparison to nootropics. The reduced ability of the treated mice to increase running wheel activity during the test sessions we want to underline because it was seen independently from the mice-type used. Antidepressants also induced common effects in both mice types considering the open field parameter place utilization. The results of antidepressant analysis suggest a deterioration of explorative behaviour essentially for rodents unlike the effects of nootropics. This was especially true for des and might be caused by the sedative nontype dependent effects of antidepressants. But the doses used were rather small and similar to therapeutic treatment because of the long-term application via drinking water.

In summary, we can say that distinguishable responses of the nootropics can be found if sensitive behavioral tests are used. A consideration of individual dispositions seems to be of particular importance. An improvement in efficiency ("high" place utilization with "low" activity scores) of locomotor behaviour may be postulated as the result of long-term treatment with nootropics in sensitive types (HAM).

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