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Effects of an Extract of Ginkgo Biloba on Learning and Memory in Mice

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WINTER, E. *Effects of an extract of Ginkgo biloba on learning and memory in mice.* PHARMACOL BIOCHEM BEHAV **38**(1) 109–114, 1991.—The effects of an extract of Ginkgo biloba (EGb 761) on acquisition, performance, and retention of mice in an appetitive operant conditioning were investigated. The animals were trained for 30 consecutive days to acquire a two-lever response sequence followed by food reward. EGb 761 was administered daily at a dose level of 100 mg/kg PO. Drug treatment started four and eight weeks before the training and was maintained until a retention test 10 weeks after it. The results indicated that EGb 761 facilitated memory processes. EGb 761 quickened the acquisition and improved the performance of the two-response sequence: The number of correct responses was increased and correct responses were performed more frequently in the most effective manner. Besides, incorrect responses were reduced sooner and faster and to a lower level in EGb 761-treated mice. With regard to the retention EGb 761 improved the retrieval of the learned response.

Ginkgo biloba Memory Appetitive conditioning Lever press Mice

THE Ginkgo biloba extract (EGb 761) is made of the leaves of Ginkgo biloba L. It contains flavonglycosides, specific terpenoid derivates (ginkgolides A, B, C; bilobalide), proanthocyanidines and some organic acids (11). The extract has been recognized as influencing the peripheral (20) and cerebral blood flow (14). Some mechanisms of action are discussed, e.g., a desaggregation of thrombocytes through stimulating the prostacyclin synthesis, a radical scavenging effect (7–9) as well as changes in the cerebral metabolism (15) and in neurotransmitter functions (4,23).

The efficiency of EGb 761 on cerebral circulation and metabolism has been demonstrated in various models of cerebrovascular insufficiency (12,19). Cerebral insufficiency is characterized by deterioration of, e.g., vigilance, attention, and memory. Several studies with psychometric tests and EEG analysis could show that such deteriorations in human beings were improved by EGb 761 (1, 13, 24). Studies in healthy persons supported the beneficial effect of EGb 761 on vigilance and memory (22). Few investigations are present which provide references to an influence of EGb 761 on memory processes in animals (16–18). Rats were trained on an active avoidance response. After that, a microembolization was performed, which led to the development of an edema and to a temporary loss of the acquired avoidance response. In rats treated with EGb 761 the avoidance responses reappeared sooner and the edema regressed more rapidly.

The present study was to contribute to the elucidation of the efficiency of EGb 761 on learning and memory processes combined with it. These investigations were based on an appetitive operant conditioning in mice.

METHOD

Animals

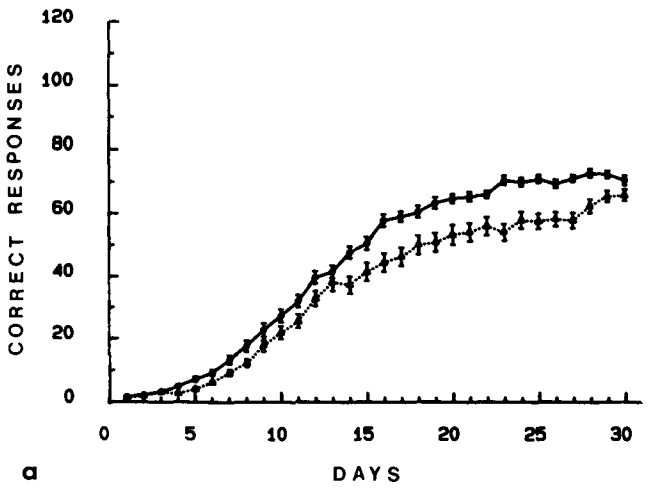
Ninety-three female albino mice of the Han:NMRI strain (Versuchstierzuchtanstalt, Hannover, F.R.G.), approximately 9 or 13 weeks old, weighing 26–30 g at the beginning of the conditioning period, served as experimental animals. All animals were inexperienced. They were housed in groups of six with water available ad lib in a temperature-controlled room (23°C) and kept on a standard diet (Altromin) of 3–4 g per animal and day. According to experience this amount guarantees a normal development of mice and a sufficient food deprivation necessary for an operant conditioning with food reward. All mice were handled daily, beginning one week before the initiation of the drug treatment, in order to attenuate their stress.

Apparatus

The experiments were carried out in an operant box (Getra). The box was enclosed in a sound-proof ventilated chamber. Centered on the front panel was a food cup, out of which 20 mg food pellets were delivered as reinforcers. Two steel levers, located at the left and the right of it, were used as manipulanda. The box was modified in such a way that the levers were deluded and could be operated only through a small fissure (5). Thus, accidental lever pressing was restricted. Further alterations of the apparatus consisted of a window for video recording at the front of the chamber.

Procedure

Operant conditioning. The experimental groups were randomly assigned either to receive EGb 761 four or eight weeks [EGb (4); EGb (8)] prior to the initiation of the conditioning period or to be kept as controls [C (4); C (8)]. The administration of EGb 761 was maintained until the retention test. All mice were exposed to



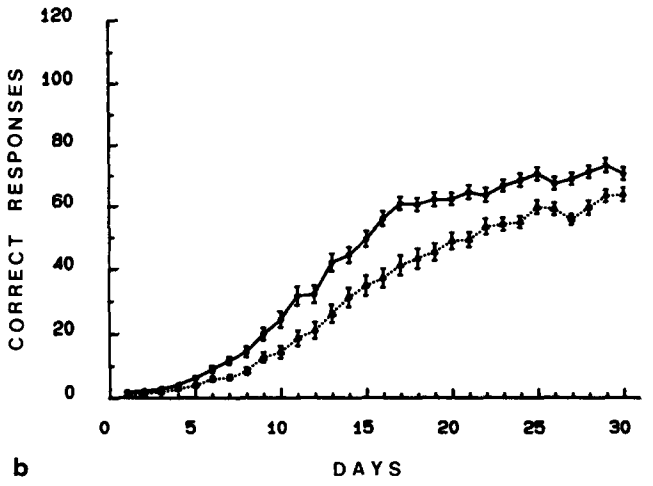
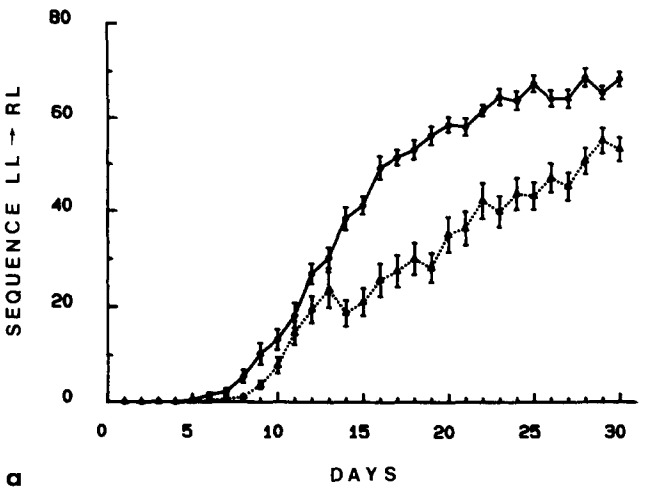


FIG. 1. The effect of EGb 761 on the number of correct responses during 30 consecutive days of a lever-press conditioning. The results are expressed as mean ± SEM per day. (a) The daily administration of EGb 761 (100 mg/kg) was initiated four weeks before the conditioning period. The level of correct responses is significantly increased by EGb 761 ($p<0.001$). EGb 761 (n = 27): ●—●; Control (n = 25): ▲---▲. (b) The daily administration of EGb 761 (100 mg/kg) was initiated eight weeks before the conditioning period. The level of correct responses is significantly increased by EGb 761 ($p<0.001$). EGb 761 (n = 18): ●—●; Control (n = 17): ▲---▲.



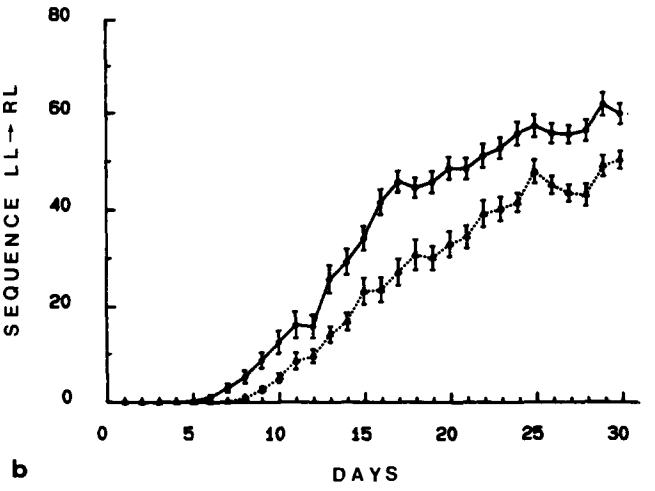
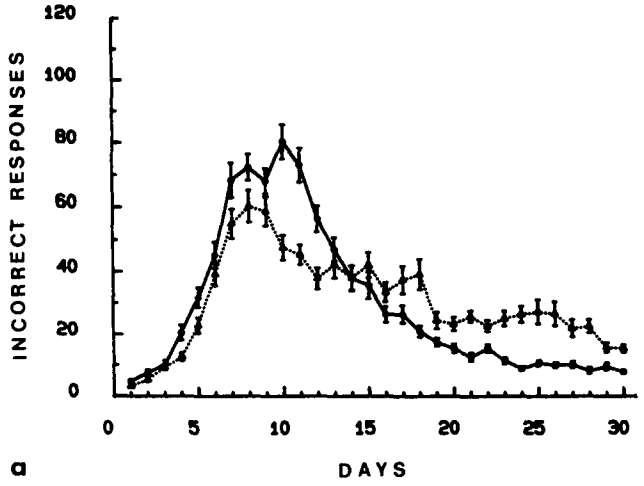


FIG. 2. The effect of EGb 761 on the number of correct responses, performed in the most effective manner (sequence of "pressing first the Left Lever, then the Right Lever, only one time each) during 30 consecutive days of a lever-press conditioning. The results are expressed as mean ± SEM per day. (a) The daily administration of EGb 761 (100 mg/kg) was initiated four weeks before the conditioning period. The level of the behavioural sequences LL→RL is significantly increased by EGb 761 ($p<0.001$). EGb 761 (n = 15): ●—●; Control (n = 14): ▲---▲. (b) The daily administration of EGb 761 (100 mg/kg) was initiated eight weeks before the conditioning period. The level of the behavioural sequences LL→RL is significantly increased by EGb 761 ($p<0.001$). EGb 761 (n = 14): ●—●; Control (n = 13): ▲---▲.

one twenty-minute session per day. Sessions were performed for 30 consecutive days.

The appetitive conditioning required the animals to press the levers in a distinct sequence for getting food reward. The mice underwent neither pretraining nor shaping to acquire the two-response sequence. Each food reward obtained by the animals was equated with a correct response. The feeding dispenser was programmed in a continuous reinforcement in case, first the left, then the right lever had been pressed. Also, repeated pressing of the two levers (e.g., five times left lever, three times right lever) led to one food reward only. Each additional lever press that was not necessary for getting reward was valued as an incorrect response. Incorrect responses could consist either of persistent pressing of one single lever or in incorrect behavioural sequences such as permanent alternation between the pressing of a single lever and the turning to the empty food cup. A lamp above the right lever lightened as soon as the sequence with the left lever was started. No other exteroceptive cues provided information concerning the correctness or incorrectness of the response. Nevertheless, during the conditioning phase, the animals alter the behaviour themselves to the most effective way of responding. This manifests itself in a decrease of behaviour that is not necessary for getting reward such as redundant ways and incorrect responses. Correct responses are performed more effectively in such a manner that left and right lever were pressed only one time each.

The process of learning is characterized by the successive development of single steps of learning, which reflect distinct strategies of learning (6). To ascertain such single steps it is not



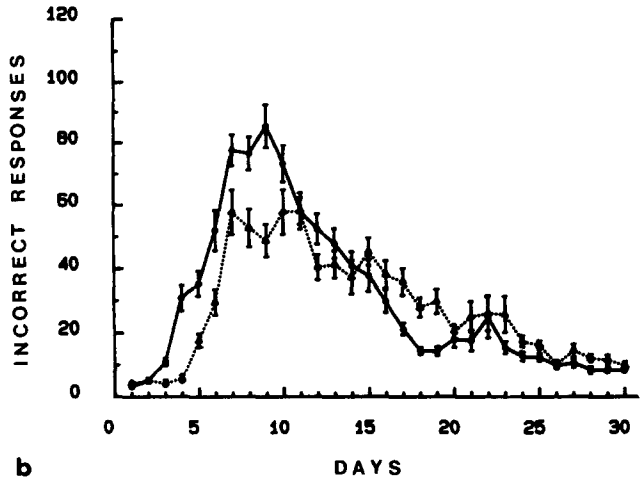


FIG. 3. The effect of EGb 761 on the number of incorrect responses as for the right lever. The results are expressed as mean ± SEM per day. For statistical evaluation the 30 consecutive days of the lever-press conditioning were separated into two periods. A two-way ANOVA was performed as well for the days 1–15 as for the days 16–30. (a) The daily administration of EGb 761 (100 mg/kg) was initiated four weeks before the conditioning period. The level of incorrect responses is significantly increased during the first and decreased during the second period by EGb 761 ($p<0.05$). EGb 761 (n=27): ●—●; Control (n=25): ▲---▲. (b) The daily administration of EGb 761 (100 mg/kg) was initiated eight weeks before the conditioning period. The level of incorrect responses is significantly increased during the first and decreased during the second period by EGb 761 ($p<0.05$). EGb 761 (n=18): ●—●; Control (n=17): ▲---▲.

sufficient to only register the number of lever presses and of food rewards. Furthermore, analysis of the response pattern has to be performed in order to evaluate the type of correct and incorrect responses.

The number of lever presses, separately for each lever, and of food rewards were automatically recorded and analyzed by all mice. Additionally, learning behaviour of 60 mice during the sessions was observed by video in order to obtain detailed information concerning the pattern of responding. Retention tests took place ten weeks after the termination of the conditioning period, lasting one session per animal. The tests examined maintenance

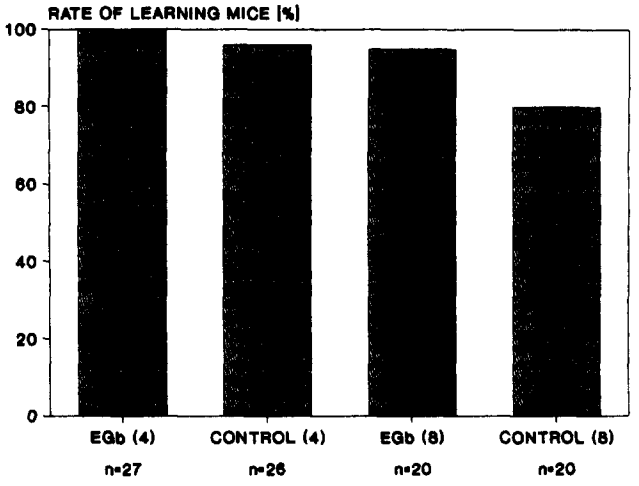


FIG. 4. The effect of EGb 761 on the speed of acquisition. The daily administration of EGb 761 (100 mg/kg) was initiated four [EGb (4)] or eight [EGb (8)] weeks before the conditioning period. Represented is the rate (%) of mice, which achieved the criterion of learning.

and retrieval of the acquired information.

The speed of acquisition was individually determined by the rate of correct to incorrect responses. Aim of conditioning was an increase of correct and decrease of incorrect responses. Criterion of having learned the two-response sequence was accomplished in case the curves, showing the number of incorrect responses, crossed that of correct ones and remained below for four consecutive days. The "day of crossing" was determined for each animal.

Activity and food intake measurements. Motor activity is of high importance in an operant conditioning. So far, the problem of the effect of EGb 761 hereupon should be elucidated. Like-

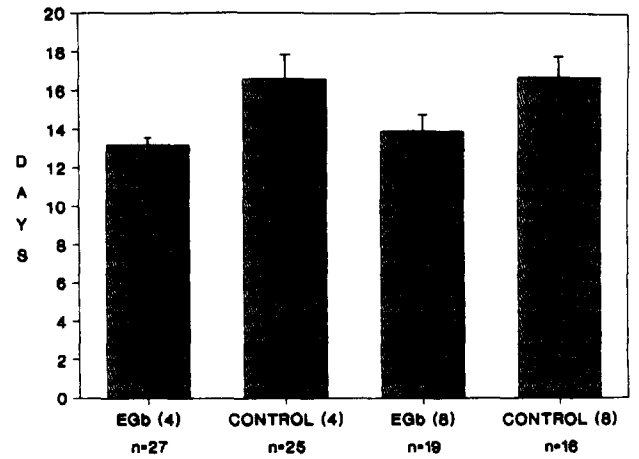


FIG. 5. The effect of EGb 761 on the speed of acquisition. The daily administration of EGb 761 (100 mg/kg) was initiated four [EGb (4)] or eight [EGb (8)] weeks before the conditioning period. Represented is the duration until the criterion of learning was achieved. The results are expressed as mean ± SEM. The speed of acquisition is enhanced in EGb 761-treated groups. The difference between EGb (8) and C (8) is significant ($p<0.05$), but not that between EGb (4) and C (4) ($p=0.06$).

TABLE 1

NUMBER OF THE CORRECT RESPONSES, OF THE BEHAVIOURAL SEQUENCES LEFT LEVER→RIGHT LEVER, AND THE DURATION NEEDED TO PERFORM THE FIRST CORRECT RESPONSE, FOR EACH GROUP OF MICE DURING THE RETENTION TEST

Group	Correct Responses	Sequence LL→RL	Latency (s) First Correct Response
EGb (4)	34.8 ± 3.4	15.0 ± 2.5†	64.6 ± 6.2
Control (4)	24.8 ± 2.8	6.3 ± 1.6	85.5 ± 13.2
EGb (8)	34.8 ± 3.4*	19.5 ± 2.5‡	36.2 ± 5.1‡§
Control (8)	26.4 ± 2.9	6.2 ± 2.2	95.2 ± 21.5

Means ± SEM. Statistical analyses were carried out with U-test of Mann-Whitney. *Different from control (8) ($p<0.05$); †different from control (4) ($p<0.01$); ‡different from control (8) ($p<0.001$); §different from EGb (4) ($p<0.01$).

The daily administration of EGb 761 (100 mg/kg) was initiated four [EGb (4)] or eight [EGb (8)] weeks before the conditioning period and was maintained until the retention test.

wise, the drug influence on food intake had to be investigated because the experiments were based on operant conditioning with food reward. Activity measurements were performed in a soundproof room by an electronic activity monitor (Stoelting, Chicago). A sensorplatform generated electro-magnetic fields, which were interrupted by locomotor activity of the mice. The number of activity counts was summed up per day. The investigation happened in four groups, respectively, two weeks without and four weeks with EGB 761 treatment.

Food intake measurements took place in four control groups and in four EGb 761-treated groups. The treatment was initiated ten weeks before the measurements. Each group, consisting of five mice, received 35 g food/day. The amount of food eaten by the groups was measured daily for four weeks.

Drugs

EGb 761 was supplied by Dr. Willmar Schwabe (Arzneimittel, Karlsruhe, F.R.G.). A mean dose of 100 mg/kg body weight, dissolved in drinking water, was administered daily. The water consumption of the mice was registered daily. It yielded the basis of calculation of the solution concentration. EGb 761 treatment extended to a period of 18 or 22 weeks.

Statistical Analysis

The behavioural results were expressed as means. Statistical analysis was worked out by using a two-day analysis of variance (ANOVA) for repeated measures (25). Significance between means was determined by the two-tailed U-test of Mann-Whitney (21).

RESULTS

Effect of EGb 761 on the Performance

The number of correct responses during 30 consecutive days of conditioning are shown in Fig. 1. The number of correct responses is higher in either EGb 761-treated groups compared with the controls. The two-way of ANOVA yielded significant differences as well between EGb (4) and C (4) as between EGb (8) and C (8) ($p<0.001$).

Correct responses performed by the behavioural sequence of "pressing first the Left Lever, then the Right Lever, only one time each" (LL→RL) can be noticed in Fig. 2. It reflects the most effective way of responding. The course of these curves resembles that of the correct responses but on a lower level. The number of most effective responses is higher in the EGb 761-treated groups than in the controls. Analysis of variance indicated significant differences as well between EGb (4) and C (4) as between EGb (8) and C (8) ($p<0.001$).

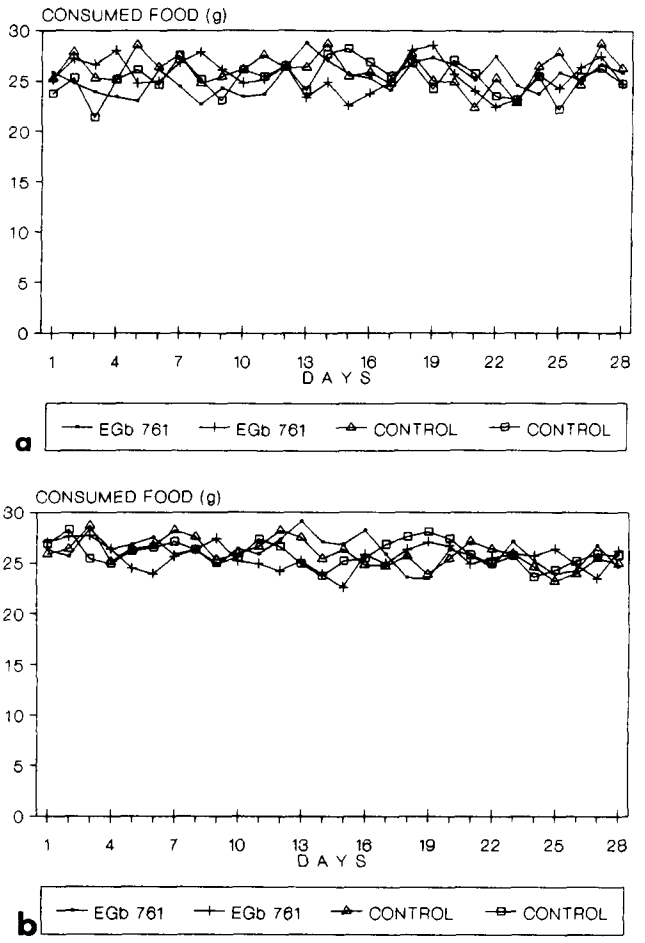


FIG. 6. The effect of EGb 761 on the food intake. Represented is the amount (g) of food eaten daily by groups of five mice. In the treated groups the daily administration of EGb 761 (100 mg/kg) was initiated ten weeks before the food intake measurements. No significant differences between EGb-treated groups and controls could be established. Mean ± SEM: EGb 761 (·) (a) 25.3 ± 0.3; (b) 26.1 ± 0.3. EGb 761 (+) (a) 25.5 ± 0.3; (b) 25.6 ± 0.2. Control (△) (a) 26.1 ± 0.3; (b) 25.9 ± 0.2. Control (□) (a) 25.3 ± 0.3; (b) 25.9 ± 0.2.

The number of incorrect responses as for the right lever is shown in Fig. 3. It shows that in the EGb 761-treated groups, approximately during the first half of the conditioning period, the level of incorrect responses is higher, during the second half lower, than in the controls. In order to evaluate either periods separately, analysis of variance was performed as well for the days 1–15 as for the days 16–30. It revealed significant differences refering to both conditioning phases ($p<0.05$) between EGb (4) and C (4) and between EGb (8) and C (8).

Effect of EGb 761 on the Speed of Acquisition

The rate of EGb 761-treated mice which have accomplished

TABLE 2

EFFECT OF EGb 761 ON THE ACTIVITY. REPRESENTED ARE DAILY MEANS ± SEM OF ACTIVITY COUNTS (n = 7 DAYS) FOR FOUR GROUPS

Week/Group	I	II	III	IV	V	VI
				EGb 761 Treatment		
I	81612 ±2513	82470 ±2168	80967 ±2324	83078 ±2578	82220 ±2245	81865 ±2436
II	85342 ±2387	84758 ±1965	84490 ±2223	84956 ±2175	85102 ±2267	85243 ±2099
III	90423 ±2759	88714 ±2712	89530 ±2760	88250 ±2648	89115 ±2804	87948 ±2748
IV	86825 ±2976	87530 ±2617	88356 ±2734	86980 ±2805	89419 ±2858	87992 ±2773

Measurements were performed for six weeks: two weeks without and four weeks with EGb 761 treatment. No significant differences between the values measured during the period without treatment and those during EGb 761 treatment could be established.

the criterion of learning the two response sequence is higher than that of the controls (Fig. 4). Six mice did not fulfil the criterion: there was one animal with EGb 761 treatment to five controls.

The duration for task solution of respectively the entire group is shown in Fig. 5. The speed of acquisition is enhanced in groups with EGb 761 treatment. They acquired the response sequence about three days earlier. U-Test revealed a significant difference between EGb (8) and C (8) ($p<0.05$). Contrary to this, the difference between EGb (4) and C (4) failed to be significant ($p=0.06$).

Effect of EGb 761 on the Retention

Ten weeks after the termination of the conditioning period the performance was deteriorated in all animals. Correct responses declined generally to about half of the level achieved during the conditioning phase. EGb 761-treated mice performed more correct responses than the controls (Table 1). U-Tests revealed significant differences between EGb (8) and C (8) ($p<0.05$) but not between EGb (4) and C (4) ($p=0.06$).

Correct responses performed by the most effective way of responding are shown in Table 1, represented by the behavioural sequence LL→RL. The frequency of these sequences is higher in either groups treated with EGb 761 than in the controls. According to U-tests the differences proved to be significant [EGb (4) vs. C (4) $p<0.01$; EGb (8) vs. C (8) $p<0.001$].

A specific criterion of retention was the time required for the performance of the first correct response. The corresponding latencies (s) can be seen in Table 1. EGb 761-treated mice needed less time to perform the first correct response compared with the controls. U-Tests yielded that the difference between EGb (8) and C (8) is significant ($p<0.001$) but not between EGb (4) and C (4).

Effect of EGb 761 on Activity and Food Intake

The number of activity counts per day are shown in Table 2. No significant differences between the weeks without and those with EGb 761 treatment could be established.

The amount of the daily consumed food can be seen in Fig. 6. The curves show no evident difference between the EGb 761 treated groups and the controls.

DISCUSSION

The present study was intended to investigate the effect of chronic EGb 761 treatment on learning and memory in mice. The results indicated that EGb 761 improved acquisition, storage, and retrieval of a two-response sequence for food reward. Response pattern normally obtained by mice responding to such lever press task were modified by EGb 761. Generally, the number of responses increased sooner. As for the incorrect responses, the increase took place sooner and came up to a higher level in EGb 761-treated mice than in the controls. This fact speaks for a quicker realization of the significance of lever pressing in order to get the reward, which may be due to an improvement in sensory registration and in motor processes. Besides, the association of the necessity of pressing both levers developed faster in EGb 761-treated mice; it became obvious by the correct responses which were increased likewise sooner.

Generally, EGb 761-treated mice showed as well more frequently as sooner a behaviour which is useful for acquiring the two-response sequence. This led to an acceleration of the speed of acquisition on an average for about three days as to a decrease of the rate of animals which did not learn the task at all. Furthermore, mice treated with EGb 761 performed the two-response sequence more frequently in the most effective way of responding than the controls. Incorrect responses and redundant ways occurred less frequently in EGb 761-treated animals. The results lead to the assumption that EGb 761 can alter the memory storage, perhaps as a consequence of the improvement of sensory registration.

Furthermore, EGb 761 caused alterations in the retrieval. Thus, the time required for performing the first two-response sequence (correct response) during the retention test was largely lowered. An improved retention by EGb 761 manifested itself in the increased number of correct responses and in the way of performing them.

The beneficial effects of EGb 761 on the operant conditioning cannot be based upon the fact that the treated mice were hungrier and therefore more motivated to perform the responses. The results of the food intake measurements speak against that. Likewise, an enhancement of the locomotor activity is to exclude.

The investigations showed that an extension of the treatment period intensified the effect of EGb 761, but is not necessary for an efficiency in general. Thus, alterations in memory processes

could be established in mice, 9 [EGb (4)] and 13 weeks of age [EGb (8)]. On principle, the findings are different to those of Continella and Drago (10) who trained rats, 8 and 24 months old, and administered EGb 761 acute and subchronic (25 and 50 mg/kg) on several avoidance conditionings. They indicated an improvement of the acquisition and retention only in the older rats, 24 months of age. The hereof differing present findings might be due to the chronic treatment and to the kind of experiments, long-term conditioning without employing of shock.

It may be assumed that the beneficial effects of EGb 761 on learning and memory refer to several mechanisms. Thus, EGb 761 efficiency may be related to the influence on neurotransmitters. Taylor (23) stated that chronic treatment with EGb 761 increased the binding and density of the muscarinic acetylcholine receptors in the hippocampus of aged rats. Besides, EGb 761 is supposed to interact likewise with vascular catecholaminergic systems: EGb 761 could potentiate the contractile action of norepinephrine, but not that of serotonine or dopamine in isolated rabbit aorta (2,3). Chronic treatment of EGb 761 led to a decrease in the density of β-adrenoreceptors (^{3}H-DHA) binding in the cerebral cortex (4).

Changes in the cerebral metabolism by EGb 761 may also contribute to the improvement of memory processes. Several studies indicate that in rats EGb 761 normalized metabolic alterations, caused by hypoxic or hypobaric hypoxia: the brain glucose level was enhanced by EGb 761, and the lactate level was remained comparatively less. The decrease in the kreatine-phosphate and ATP level combined with hypoxia did not occur in EGb-treated rats (15,19).

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