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Behavioural Effects of Etiracetam in Rats

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WOLTHUIS, O. L. *Behavioural effects of etiracetam in rats.* PHARMAC. BIOCHEM. BEHAV. 15(2) 247–255, 1981.— The effects of etiracetam, a structural analogue of piracetam, were investigated in rats on Y-maze discrimination acquisition, on open field behaviour, on one-trial passive avoidance learning and on shuttlebox acquisition and extinction. The results indicate that this drug significantly enhances acquisition and may improve retention without having any detectable effects on spontaneous behaviour, not even in very high doses (500 mg/kg IP). Sensitivity to footshock, measured as "flinch" thresholds, was not altered by etiracetam in doses of 25 or 100 mg/kg IP. For a shuttlebox task the effective dose-range lies between 20–30 mg/kg IP, provided pretreatment during 4 days is given. Without pretreatment, i.e. when the drug is only administered during the relatively fast acquisition in the shuttlebox, it was found that acquisition was not enhanced, but extinction of the acquired behaviour was significantly inhibited. The effects of etiracetam can be found at lower dose-levels than with piracetam and also in tests (passive avoidance, shuttlebox) in which piracetam has no or only marginal effects.

Etiracetam Piracetam Acquisition Extinction Retention Open field

ETIRACETAM is a closely related structural analogue of the acquisition enhancing drug piracetam (UCB 6215) that has been extensively studied in a number of laboratories. The interest in piracetam, a virtually nontoxic drug, has been focussed on positive effects on learning and memory processes and on the underlying mechanisms [6, 7, 8, 10, 20, 21]. The attempts to analyse the acquisition enhancing effects of piracetam so far have shown that the compound enhances transcallosal potentials [9], visually evoked potentials [21], cortically evoked potentials following toothpulp stimulation [12] and also facilitates interhemispheric visual information transfer [3]. It is tempting to suggest that the compound affects information processing during the first phase of data handling in the brain, i.e. the "registration" or "writing in" phase, although other effects may be possible [5,18].

On the biochemical level, piracetam stimulates in vitro leucine uptake by cerebral cortex slices and inhibits breakdown of newly formed protein in these slices, but it has no effect on the incorporation of leucine into cerebral proteins, neither in vitro nor in vivo [17]. The drug has also no effect on cerebral energy metabolism under normal conditions, although it may have a beneficial effect during hypoxia by virtue of its adenylate kinase (E.C. 2.7.4.3) stimulating action [16]. In view of the possible role of proline as an inhibitory transmitter in the rat cerebral cortex [2] it is of interest that piracetam inhibits the calcium-dependent proline release from slices of the visual, but not from those of the parietal brain cortex of the rat [15]. When this occurs also in vivo, one might speculate that piracetam-induced facilitating processes in the brain cortex may result from a reduced release of inhibitory transmitter. Whatever the mechanisms of action may be, it is clear that the effects of piracetam in rats can only be obtained with relatively high doses. In our hands repeated attempts to obtain reliable dose-response effects failed. Therefore, it was interesting to test several structural analogues in a number of behavioral tests. The results obtained with one of these analogues, now given the generic name of etiracetam [8], are reported here.

METHOD

Animals

Male small Wistar (WAG/Ry) rats with a bodyweight of 150–170 g and an age of $2^1/_2$–3 months were used in all experiments. The rats are raised under SPF conditions, i.e. hysterectomy derived, reared behind a germfree barrier and bacteriologically controlled (for details see [1]). They are kept in the experimental animal room when not tested. This room is humidity regulated (70–80%), temperature controlled (22–23°C) and lighting is on a 12 hr "on"–12 hr "off" schedule, switched at 7:00 a.m. and 7:00 p.m. Food and water were supplied at lib.

Apparatus

Groups of animals were tested in an automated open field, in a capacitance activity measuring device and their response thresholds to inescapable footshock were determined. Furthermore groups of animals were trained in a Y-maze, in a two-way automated shuttlebox and in a two compartment passive avoidance apparatus.

Measurements of Movements in an Open Field Situation and of Motor Activity in a Capacitance Device

The automated open field technique was developed in our laboratory by Tanger *et al.* [19]. Basically it consists of a

television camera scanning the movements of a white rat in a black field of 1 m^2. The x and y coordinates of the rat are sampled 50 times per sec, registered on paper tape and subsequently analysed by computer. When these experiments were done, the combination of this system with an earlier developed capacitance system [22] had been completed, so that in essence open field behaviour could be measured three-dimensionally (see Fig. 1). Three groups of 6 rats each were injected IP 30 min prior to testing with saline, piracetam (200 mg/kg) or etiracetam (100 mg/kg). A fourth group received methamphetamine, 2 mg/kg IP. Each animal was tested during a full hour following the injection. The whole experiment was repeated once with 4 groups of 6 different rats each and the results of both experiments were pooled. Two earlier experiments had been performed in which motor activity was measured using a capacitance technique [22]. In the first experiment 4 groups of 8 rats each were injected with either saline, piracetam (150 mg/kg), etiracetam (100 mg/kg) or methamphetamine (2 mg/kg). In the second experiment 3 groups of 8 rats each were injected with either saline or etiracetam (250 or 500 mg/kg). The injections took place after control measurements of activity had been made during 16 min. After the animals had been briefly taken out of the apparatus for the IP injection the measurements were continued for 80 min.

Response Thresholds to Inescapable Footshock

Three groups of 6 rats each were tested 30 min after the IP injection of either saline or etiracetam in doses of 25 or 100 mg/kg. The procedure followed was identical to the one described before [20]. Briefly, for each animal the flinch response threshold was measured by an up and down method. Responses were recorded when all 4 paws were in contact with the grid floor. Testing occurred in a randomised order and in a "blind" fashion. The shock scramblers used in the present experiments, however, were newer in design and generated 7 msec constant current pulses, scrambled over 10 grid rods. The shock scramblers were constructed by the electronic department of the Medical Biological Laboratory TNO to obtain shock delivery of high precision. The parameters of shock delivery are different from those used before.

Y-Maze Discrimination Learning

The device is the same as described before [20]. Three groups of 6 rats each were trained 2×5 days, with a weekend in between. Saline (0.9% NaCl), piracetam (150 mg/kg) or etiracetam (100 mg/kg) was administered intraperitoneally (IP) 30 min prior to the start of 6 consecutive daily trials. Each rat was trained to avoid shock by going into the illuminated alley within 10 sec after the exit of the start compartment had been opened. Either the right or the left alley was illuminated according to a Gellerman sequence. Intertrial intervals were approximately 30 sec and footshock intensity was 240 μA (constant current). Three of such experiments have been performed, the first consisted of 3 groups of 6 rats each, the second of 2 groups of 6 rats each (saline or etiracetam-treated respectively, a third group of 6 rats was not treated with piracetam but with another product) and the third experiment consisted again of 3 groups of 6 rats each. The results of the three procedurally identical experiments were pooled.

Two Compartment Light-Dark Passive Avoidance

The compartments consisted of two symmetrical Plexiglas cages (30×30×30 cm each), standing on a shock grid and connected by a gate with a pneumatically operated guillotine door guarded by four infrared light beams. One compartment was dark, the other was illuminated by a small fluorescent tube. The four light emitting diodes which generated the infrared light were mounted two by two on the light and the dark side of the door. On each side the distance between the upper and the lower light was 1 cm. Both beams were interrupted by the animal's head or body, but tail movements in the door opening could, on one side of the door, only interrupt one beam at a time. Thus, by sequential interruption and reinstatement of beam continuity on both sides of the door, the detection of movements of the animal could be registered without false detections by tail flicks. The equipment, built in the laboratory, registered the following 4 parameters: the latency until entering the dark compartment, the time spent in the dark compartment per period of 3 min, the number of times the animals changed compartments and the number of approaches into the dark compartment. An approach (followed by a retreat) causes a different sequence of interruption than a change of compartments, this is electronically sorted out and registered accordingly on paper tape. The principle of the test is well known. When given a choice a rat exhibits a preference to stay in the dark compartment. Once it has received a footshock in the dark compartment, however, it tends to avoid this compartment initially but after a long latency period it may enter this compartment again. Four experiments were carried out, each with 4 groups of 4 rats. The first two experiments each contained in addition two piracetam-treated groups of 4 rats, i.e. one non-shocked group and a group which received footshock, which were treated identical to the etiracetam-treated rats. The results obtained with identically treated animals were pooled. The procedure was as follows, each animal received 3 IP injections of saline, etiracetam (50 mg/kg) or piracetam (150 mg/kg), one injection per day. On the fourth day, 30 min prior to training, the animal received the fourth injection. Subsequently the animal was placed in the illuminated box with its head facing away from the gate. When the animal had entered the dark compartment, the guillotine door was closed automatically by a pneumatic device constructed in a way which prevented damage to the tail. The door remained closed for 15 sec during which period the animal received a scrambled footshock of 250 μA (constant current). Only the experimental groups treated with either saline, etiracetam or piracetam received footshocks, the three similarly treated control groups did not. After 15 sec the door opened again, the rat escaped to the illuminated compartment and was returned to its home cage after it had calmed down (15–30 sec). The next day each animal was tested during 30 minutes and the same four parameters were registered.

Experiments with the Automated Two-Way Shuttlebox

The dimensions of the two-box devices were identical to those of the passive avoidance apparatus. The two compartments were standing on a shock grid and were connected by a gate guarded by 4 infrared light beams, there was no door. A signal light was mounted in the top of each cage. In the acquisition experiments each rat received 20 trials daily, during which the animal had to learn to avoid shock by moving into the other compartment within 10 sec after the signal in the first compartment had been turned on. The light went out when the rat had passed through the gate. The intertrial

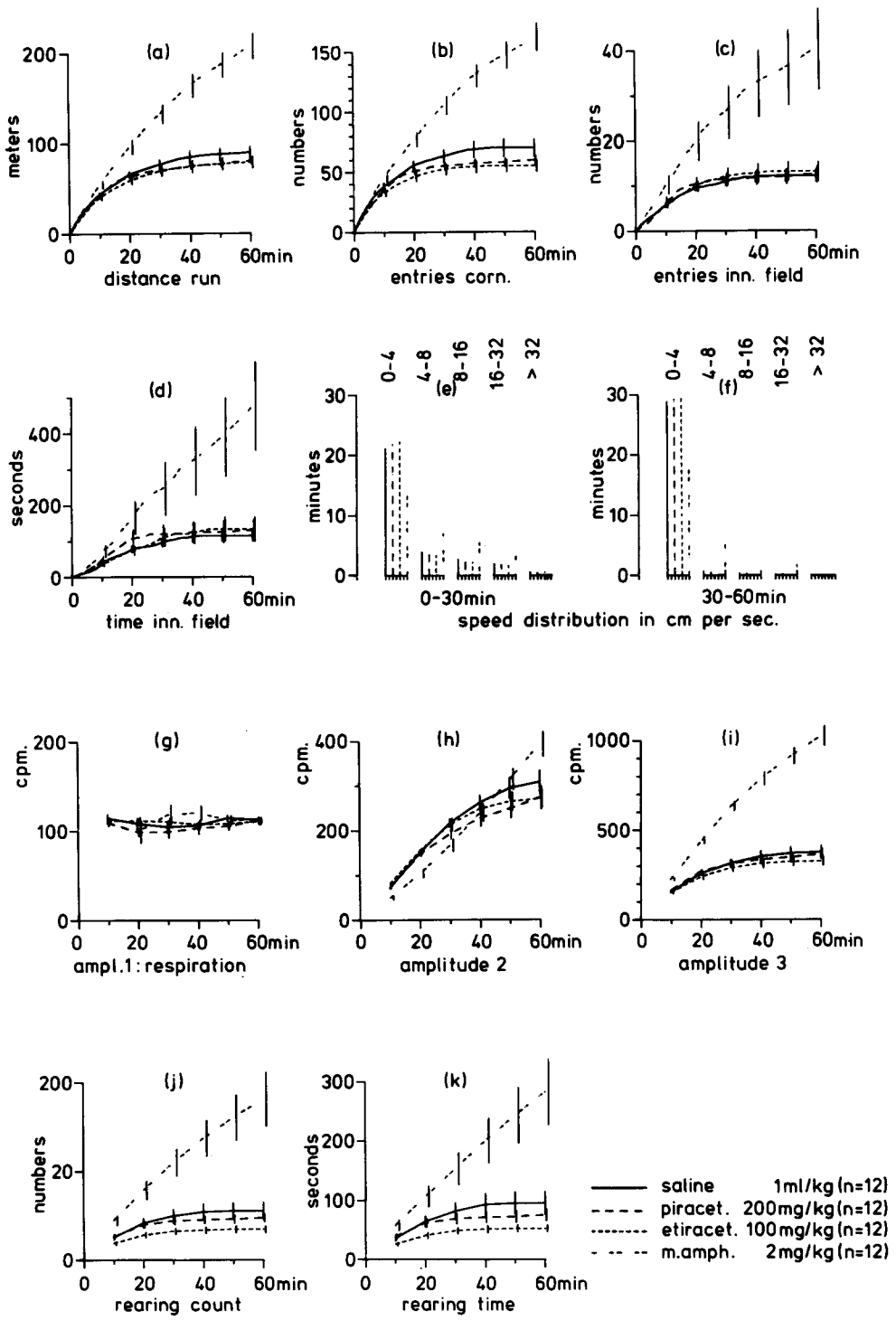

FIG. 1. Automated open field measurements of rats starting 30 min after the IP injection of various solutions. Behaviour of saline-, etiracetam- and piracetam-treated rats does not differ significantly in any of the parameters measured, whereas after methamphetamine the increase in motor activity dominates in each graph. The effects of methamphetamine differ significantly ($p<0.05$, two tailed) from each of the other 3 treatment groups except in the measurements of respiration (graph g) and of the vertical components of small movements (graph h). All graphs, except graph g represent cumulative data. Graph a: distance run in meters; graph b: number of entries into corner sections (20×20 cm); graphs c and d: number of entries into the inner field (60×60 cm) and the time spent there respectively; graphs e and f: the time that speeds of movements, subdivided into speed classes, are sustained during the first (e) and the second (f) half of our testing; graph g: respiration rate in counts per minute (cpm); graphs h and i: number of small (h) and larger movements (i) respectively; graphs j and k: the number of rearings (j) and the time spent in an upright position (k) respectively. The vertical bars represent S.E.M.

interval was 1 min (±20% random) and the footshock intensity 250 μA (constant current). When the animal failed to escape, footshock was turned off after 20 sec. To evaluate "within session" learning each session of 20 daily trials was artificially subdivided into 2 blocks of 10 trials. When the animal had made 8 or more correct avoidances in two successive blocks of 10 trials (within or between sessions) it had reached criterion.

Each animal was drug pretreated once daily for 3 days prior to the start of the training, doses were identical to those administered during training. During training each animal received the solutions as an IP injection, 30 min before the daily training session. In total, 6 procedurally identical experiments were carried out; only the doses in the groups varied. Two experiments were done with 3 groups of 6 rats injected with either saline (0.9 NaCl solution), 30 or 40 mg/kg etiracetam, respectively. Three experiments each with 4 groups of 6 rats treated with saline, 10, 20 or 40 mg/kg etiracetam, respectively. One experiment consisted of two groups of 12 rats each, injected with saline or 25 mg/kg etiracetam. Proceeding these experiments, similar acquisition experiments had been carried out repeatedly with piracetam with pretreated groups of 6 rats and at dose levels of 100 or 150 mg/kg IP.

In experiments where extinction was tested the rats were trained in exactly the same manner as in the acquisition experiments, except that the rats were not pretreated. The animals were only injected during acquisition, not during extinction. In the extinction phase footshock was not turned on when the animal failed to avoid. The criterion for acquisition was the same as in the acquisition experiments, the criterion for extinction was reached when the animal failed to avoid in 60% or more of the trials in two successive blocks of 10 trials (within or between sessions). Only one dose-level of etiracetam was used: 25 mg/kg IP, the control animals received the same volume of saline. Two identical experiments were carried out, each with 12 experimental and 12 control animals, the results of which were pooled.

Statistics

The open field data were analysed according to Kruskall and Wallis [11], followed by the simultaneous statistical interference method of Dunn, adapted according to Newman-Keuls [13]. The same methods were used for the Y-maze data and the results of the shuttlebox experiments on acquisition. For the passive avoidance tests the data on "latencies" were analysed according to Welch [14] and the data on "dark box time per 3 min" were analysed with the method of Scheffé [13]. Finally, the results of the shuttlebox experiments on extinction were analysed according to Fisher [14]. All statistical testing occurred with an $\alpha=0.05$, two tailed.

Substances

Piracetam and etiracetam were generously donated by U. C. B., Brussels. Methamphetamine HCl was obtained commercially.

RESULTS

The effects on spontaneous motor behaviour in an open field situation are shown in Fig. 1. Etiracetam and piracetam, in doses of 100 and 200 mg/kg IP respectively, have no effect on any of the 11 parameters measured, while the rats treated with a moderate dose of methamphetamine (2 mg/kg IP)

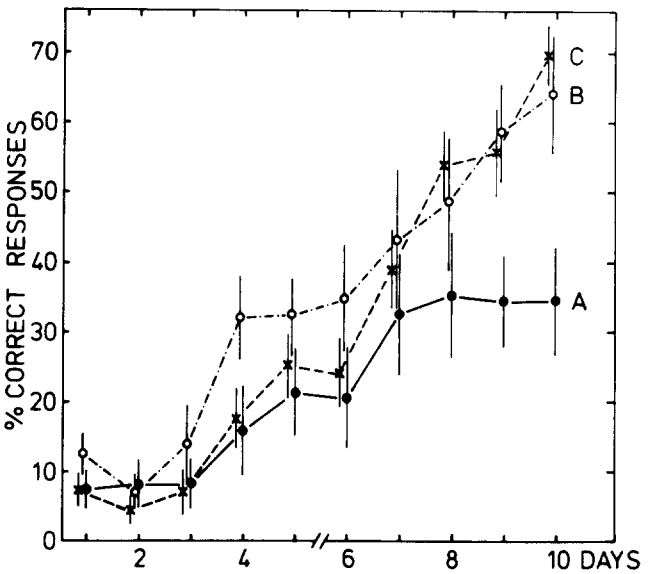

FIG. 2. The effects of etiracetam and piracetam on Y-maze discrimination learning of rats. Injections were given IP, 30 min prior to each daily training session of 6 trials, interrupted during the weekend. The differences between the acquisition curves of saline and drug-treated groups became significant ($p<0.05$, two-tailed) after 8 days of training. A: 0.9% NaCl, 1 ml/kg, n=18; B: piracetam, 150 mg/kg, n=12; C: etiracetam, 100 mg/kg, n=18.

clearly show increased motor activity. The effects of saline, piracetam and etiracetam did not differ significantly whereas the effects of methamphetamine differed significantly ($p<0.05$, two tailed) from all three other groups, except in breathing frequency (graph g) and in the cumulative record of small movements (graph h). Measurements of the effects of etiracetam and piracetam on spontaneous movements in the more confined space of the capacitance device gave equally negative results, even when etiracetam was administered in doses of 100, 250 or even 500 mg/kg IP. Methamphetamine induced the same effect as reported before [22].

The flinch response thresholds to inescapable footshock were not altered by etiracetam. The mean (±S.E.M.) thresholds for each of the 3 groups of 6 rats each were 159±9.2, 165±4.5 or 159±6.8 μA following treatment with saline, etiracetam 25 mg/kg IP or etiracetam 100 mg/kg IP respectively. These values are considerably higher than those found previously [20], which is due to the changed parameters for footshock delivery.

The results of the Y-maze experiments are shown in Fig. 2. When this particular training procedure is employed, in which only 6 daily trials were given to each animal, acquisition of saline-treated animals is very slow and leaves much room for improvement. Acquisition of the discrimination task is enhanced by etiracetam (100 mg/kg IP). In these experiments the animals were not pretreated prior to the training period and the difference between experimental and control groups becomes significant ($p<0.05$, two tailed) after 8 days of training (Fig. 2). In the doses applied the effects of etiracetam and piracetam on acquisition were approximately equal.

The results from the passive avoidance presented in Fig. 3, show that etiracetam has no significant effects on the behaviour of animals which did not receive a footshock. On the

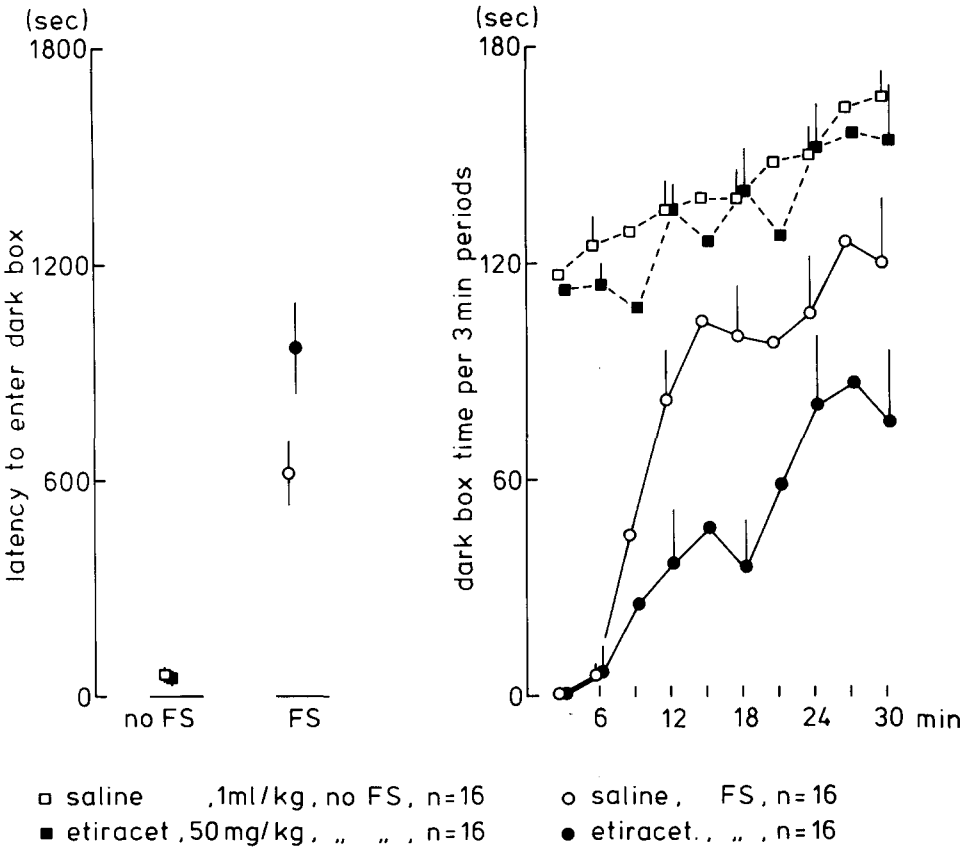

FIG. 3. The results of light-dark passive avoidance testing, 24 hours after one trial learning. Each rat received 4 IP injections on 4 consecutive days, the last injection was given 30 min prior to training. Etiracetam improved retention; following training the latency to enter is significantly ($p<0.05$, two-tailed) increased and, measured per 3 min periods during min, the drug-treated rats spend a significantly ($p<0.05$, two-tailed) smaller amount of time in the dark compartment. The experiment contained four treatment groups, each of n=16: □ saline, 1 ml/kg, no footshock (FS); ■ etiracetam, 50 mg/kg, no FS; ○ saline+FS and ● etiracetam+FS. The vertical bars represent S.E.M.

other hand, the drug caused a significant ($p<0.05$, two tailed) increase in the latency to enter the dark box in animals which did receive a footshock. Measured cumulatively during periods of 3 min, this trend was consistent during the subsequent period of 30 min; i.e. etiracetam-treated animals spent a significantly ($p<0.05$, two tailed) smaller amount of time in the dark box. This occured in spite of the fact that the mean number of approaches in the etiracetam-treated rats during those 30 min was greater than in the control animals, 93 versus 69, respectively. Each of the first two of the four successive experiments also contained two groups of rats treated identically with piracetam (150 mg/kg). Since this treatment appeared to have hardly any effect at all, piracetam-treated groups were not included in the last two of the four experiments and the results are not shown in the graphs.

The results of the acquisition experiments with the shuttlebox were very consistent. They are presented in two ways: (a) the number of animals per group that reached criterion plotted versus the number of daily sessions of training. This was done for each of the three experimental series with different dose regimens (Fig. 4A, B and C) and (b) the mean (±S.E.M.) number of trials to reach criterion plotted versus the dose of etiracetam (Fig. 4D). The latter graph presents the pooled data from all 6 experiments, which were performed in a nearly alternating order to eliminate possible time dependent factors. The results of the saline-treated control animals for each of three experimental series with different dose regimens are shown separately in this graph. It can be seen that etiracetam has a clearcut positive effect on acquisition, and that the drug has an optimal dose range of 20–30 mg/kg IP. The effects of 20 and 25 mg/kg differed significantly ($p<0.05$, two tailed) from that of saline. In similar experiments, also with pretreatment during several days, piracetam in doses of 100 or 150 mg/kg IP caused no significant effects.

In the extinction experiments with the shuttlebox no pretreatment was given. The results, given in Fig. 5, show that under those conditions enhancement of acquisition does not occur whereas extinction is significantly ($p<0.05$, two tailed) inhibited. There appears to be no correlation between the speed of extinction and the speed of acquisition for individual animals. Extinction is at first partial; it takes more than 4 weeks before total extinction is achieved.

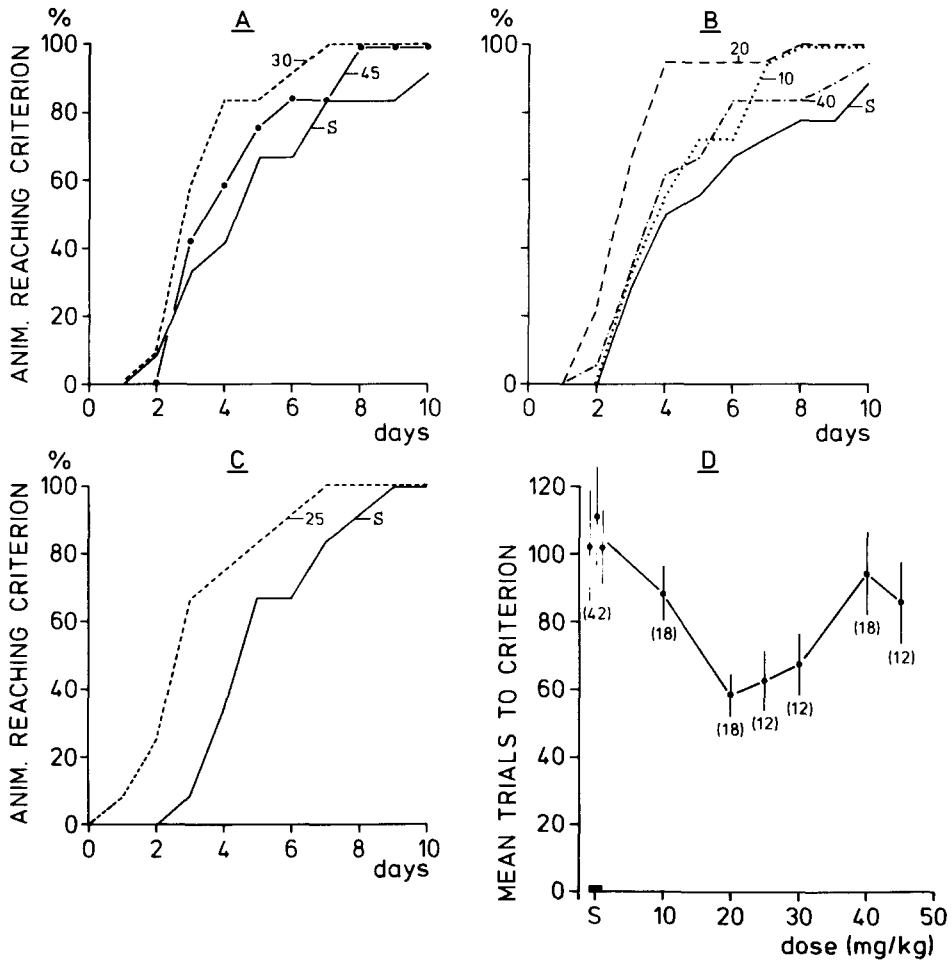

FIG. 4. The effects of different dose levels of etiracetam on shuttlebox acquisition. Each animal was injected IP 30 min before each daily training session of 20 trials and all animals were pretreated with one daily injection during 4 consecutive days prior to the start of training. Doses of 20, 25 and 30 mg/kg caused a significant ($p<0.05$, two-tailed) enhancement of acquisition. The results are expressed in two ways. Graphs A (2 experiments), B (3 experiments) and C (1 experiment) show the results as the number of animals reaching criterion versus days of training; the doses in mg/kg are shown with each curve (S=saline), the experiments were performed in a nearly random order. Graph D shows the combined results expressed as the mean (±S.E.M.) number of trials versus the dose of etiracetam, the total number of rats tested at each dose level are shown in parenthesis. The values of saline-treated control groups from graphs A, B and C are individually shown in graph D.

DISCUSSION

The results of the present experiments indicate that in the rat etiracetam enhances acquisition more effectively than piracetam. In the Y-maze experiments etiracetam in a dose of 100 mg/kg causes approximately the same enhancement as piracetam in a dose of 150 mg/kg. Surprisingly, the dose of etiracetam with which the animals are treated before and during shuttlebox acquisition has to be reduced to 20–30 mg/kg IP to obtain optimal effects. Under similar conditions piracetam in IP doses of 100 or 150 mg/kg has no effects and unpublished results of dose-range finding attempts, also with lower and higher doses of piracetam, make it unlikely that piracetam has a significant effect on shuttlebox acquisition.

When etiracetam (25 mg/kg) is only administered during shuttlebox training and pretreatment with etiracetam is omitted, the animals do not acquire the shuttlebox task faster, but when treatment is stopped and the footshock reinforcement is discontinued, subsequent extinction is significantly ($p<0.05$, two tailed) slower in etiracetam-treated rats than in saline-treated control rats. Piracetam was not tested in this experimental procedure. However, the effects of piracetam (150 mg/kg IP) were tested in two of the four passive avoidance experiments. Since pretreatment in these first two experiments with piracetam did not cause any effect at all, piracetam was not included in the last two experiments. Animals pretreated with etiracetam (50 mg/kg IP) or saline were present in equal numbers in all four experiments. The test results show that the etiracetam-treated animals avoid the dark compartment for a significantly ($p<0.05$, two tailed) longer period than the control rats. This may indicate that etiracetam also improves retention. A definite statement in this respect cannot be made since, in contrast to shuttlebox acquisition, the "one trial" nature of the passive avoidance task does not permit us to detect whether this effect is

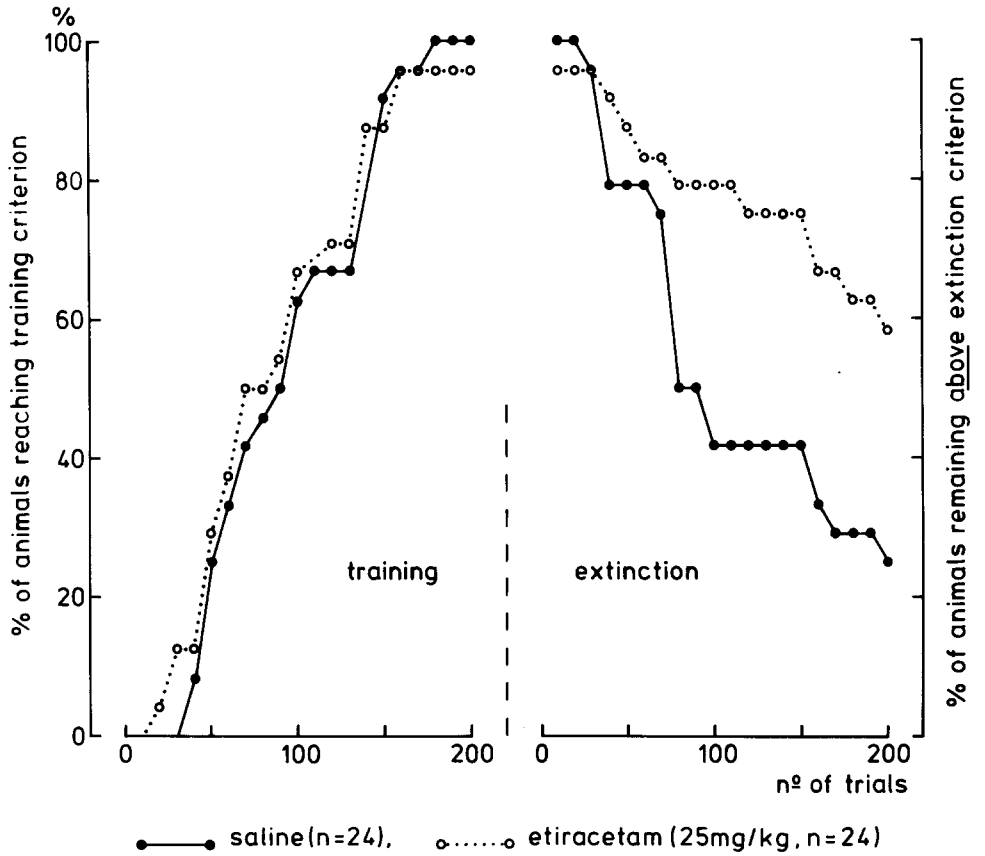

FIG. 5. The results of shuttlebox experiments in which etiracetam administration was restricted to the acquisition phase. Without pretreatment with etiracetam acquisition is not enhanced, yet extinction is significantly ($p<0.05$, two-tailed) inhibited. Twenty trials were given per day, each point represents the percentage of animals reaching the acquisition criterion (left side) or the percentage remaining above the extinction criterion (right side) following 10 trials.

caused indirectly through improvement of acquisition. As in the case of piracetam it is very unlikely that the etiracetam-enhanced acquisition is due to aspecific factors such as changes in footshock sensitivity, or to increased activity levels, tranquillizing or sedative effects. Such effects were not found, not even at high dose levels. If the mechanisms of action of piracetam and its analogue etiracetam are essentially the same, then etiracetam is a more effective drug.

Some interesting features emerge in relation to the greater effectiveness of etiracetam; these concern the dose effect relationship, the delayed action, the effect of pretreatment, the effects on extinction and a possible effect on retention. The dose of etiracetam used in the Y-maze experiments, without pretreatment, was 100 mg/kg and in the passive avoidance tests, with pretreatment, 50 mg/kg. Surprisingly, the results of the shuttlebox experiments not only show that the fastest acquisition was obtained with 20–30 mg/kg, but also that higher dose levels were less effective. The results of subsequent experiments with different dose regimens were quite consistent and there can be no doubt that this is a real phenomenon. For dose-range finding studies the shuttlebox technique is more suitable since the Y-maze experiments are laborious and passive avoidance learning, due to its "one trial" nature, makes it impossible to follow the effects on acquisition during a number of days. In view of the optimal dose-levels found in the shuttlebox experiments it is remarkable that with the comparatively high doses used in the Y-maze and passive avoidance acquisition significant effects were found at all. This may indicate that either optimal doses vary from one task to another or that even larger effects can be expected in the Y-maze and passive avoidance tests with more optimal and lower doses. The delayed effects of etiracetam and piracetam can be seen in Fig. 2, the differences in acquisition between control and experimental groups become significant after 8 days of training. This is in agreement with earlier findings with piracetam with a slightly different method of Y-maze training (10 trials per day instead of 6 [20]) and in essence also with those of Dimond [4] who found that effects of this drug on certain tasks in human volunteers were detectable after two weeks but not after one week of treatment. No explanation for this phenomenon is available. The results suggest that these drugs have to be administered during several days to start or disinhibit some metabolic machinery involved in the enhancement of acquisition. If this is true, pretreatment with the drug offers the animals a "running start" at the beginning of training. The finding that with etiracetam-pretreatment effects in the shuttlebox are detectable in the first few days and can even be detected in the one trial passive avoidance test, are in agreement with this notion. Previous results, showing that

after several days of pretreatment the effects of piracetam on evoked potentials become more pronounced [21], point in the same direction. However, if the above mentioned speculations were true one would like to understand why, without pretreatment, shuttlebox acquisition is not enhanced in a later stage of training. One explanation might be that under these conditions a positive effect of etiracetam cannot be expressed because already after 4 days more than 60% of the animals have reached the criterion and the others already perform at a 60–70% avoidance level, which leaves little space for improvement.

The results of the one trial passive avoidance test indicate that etiracetam may improve retention. Since this drug delays the animal's first entrance into the dark compartment it may not be concluded from the results that etiracetam also inhibits extinction of the acquired behaviour, because the starting points for extinction testing are not the same in the experimental and control groups. If their behaviour is not only followed during the customary 3 minutes but also during the subsequent 27 minutes, the experimental animals spend less time in the dark compartment than the control animals. This might be an indication of slower extinction but may also be a consequence of the improved retention which was already detectable in the first 3 minutes. This remains somewhat speculative, however, since the improved retention and the inhibited extinction may simply be expressions of improved acquisition; due to the one-trial nature of the task this cannot be detected and excluded.

In the shuttlebox experiments on extinction rather unexpected results were obtained. Without pretreatment acquisition was not enhanced and yet extinction was inhibited notwithstanding discontinuation of etiracetam-administration at the end of the training period. During the testing of the extinction its rate may be governed by the combined effect of two processes: (1) the "solidity" or "quality" of the programmed memory trace which induces the animal to respond with the same conditioned reaction even when this becomes apparently senseless, and (2) the relearning capacity, i.e. the capacity to acquire a new behavioural repertoir in response to a novel situation. If the latter is true, etiracetam administration exclusively during the extinction period might very well facilitate extinction by virtue of its acquisition-enhancing effect. The design and particularly the interpretation of such an experiment, however, is complicated by the fact that etiracetam has a delayed effect, as has been discussed above. For the moment it seems best to conclude that under the influence of etiracetam a more solid memory trace is formed, which dominates the animal's behaviour under the appropriate conditions and which renders it more resistant to extinction. The suggested improved retention found in the passive avoidance test is not contradictory to this conclusion.

Finally, a word of caution is perhaps necessary. In the present report etiracetam is often compared with piracetam. The reason for this is the analogy of the molecular structure of these two compounds and, at first glance, some similarities in their effects. It is far from certain, however, that the observed effects are only quantitatively and not qualitatively different.

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REFERENCES

1. Baker, H. J., J. R. Lindsey and S. H. Weisbroth, editors. *The Laboratory Rat, Volume I: Biology and Disease*. New York: Academic Press, 1979, chapter 8.
2. Balcar, V. J., G. A. R. Johnston and A. L. Stephanson. Transport of l-proline by rat brain slices. *Brain Res.* **102:** 143–151, 1976.
3. Burešova, O. and J. Bureš. Piracetam-induced facilitation of interhemispheric transfer of visual information in rats. *Psychopharmacologia* **46:** 93–102, 1976.
4. Dimond, S. J. Use of a nootropic substance to increase the capacity for verbal learning and memory in normal man. *Proceedings of the Symposium "Nooanaleptic and Nootropic Drugs"*, edited by A. Agnoli. Rome: Pozzi, 1975, pp. 107–110.
5. File, S. E., J. R. G. Hyde and F. J. Odling-Smee. Piracetam impairs the overshadowing of background stimuli by an informative CS. *Physiol. Behav.* **23:** 827–830, 1979.
6. Giurgea, C. Nootropic and related drug interacting with the integrative activity of the brain. In: *Biological Psychiatry Today*, edited by J. Obiols, C. Ballús, E. González Monclús and J. Pujol. Amsterdam: Elsevier/North-Holland, 1979, pp. 876–881.
7. Giurgea, C. Piracetam: nootropic pharmacology of neurointegrative activity. In: *Current Developments in Psychopharmacology*, Vol. 3, edited by W. B. Essman and L. Valzelli. New York: Spectrum, 1976, pp. 223–273.
8. Giurgea, C. and F. Mouravieff-Lesuisse. Pharmacological studies on an elementary model of learning. The fixation of an experience at the spinal level. *Archs int. Pharmacodyn.* **191:** 279–291, 1971.
9. Giurgea, C. and F. E. Moyersoons. On the pharmacology of cortical evoked potentials. *Archs int. Pharmacodyn.* **199:** 67–78, 1972.
10. Giurgea, C. and G. Salama. Nootropic drugs. *Prog. Neuropsychopharmac.* **1:** 235–247, 1977.
11. Hollander, M. and D. A. Wolfe. *Nonparametric Statistical Methods*. New York: John Wiley and Sons, 1973, pp. 115–119 and p. 125.
12. Krug, M., T. Ott, K. Schulzeck and H. Matthies. Effects of orotic acid and pirazetam on cortical bioelectric activity in rabbits. *Psychopharmacology* **53:** 73–78, 1977.

13. Miller, R. G. *Simultaneous Statistical Interference*. New York: McGraw-Hill, 1966.
14. Natrella, G. A. *Experimental Statistics. National Bureau of Standards Handbook 91*. Washington, D. C.: U. S. Government Printing Office, 1963.
15. Nickolson, V. J. and O. L. Wolthuis. Differential effects of the acquisition enhancing drug pyrrolidone acetamide (piracetam) on the release of proline from visual and parietal rat cerebral cortex in vitro. *Brain Res.* **113:** 616–619, 1976.
16. Nickolson, V. J. and O. L. Wolthuis. Effect of the acquisition-enhancing drug piracetam on rat cerebral energy metabolism. Comparison with naftidrofuryl and methamphetamine. *Biochem. Pharmac.* **25:** 2241–2244, 1976.
17. Nickolson, V. J. and O. L. Wolthuis. Protein metabolism in the rat cerebral cortex in vivo and in vitro as affected by the acquisition-enhancing drug piracetam. *Biochem. Pharmac.* **25:** 2241–2244, 1976.
18. Sara, S. J. and M. David-Remacle. Recovery from electroconvulsive shock-induced amnesia by exposure to the training environment: Pharmacological enhancement by piracetam. *Psychopharmacologia* **36:** 59–66, 1966.
19. Tanger, H. J., R. A. P. Vanwersch and O. L. Wolthuis. Automated TV-based system for open field studies: effects of methamphetamine. *Pharmac. Biochem. Behav.* **9:** 555–557, 1978.
20. Wolthuis, O. L. Experiments with UCB 6215, a drug which enhances acquisition in rats: its effects compared with those of methamphetamine. *Eur. J. Pharmac.* **16:** 283–297, 1971.
21. Wolthuis, O. L. and V. J. Nickolson. Piracetam and acquisition behaviour in rats: electrophysiological and biochemical effects. *Proceedings of the Symposium "Nooanaleptic and Nootropic Drugs"*, edited by A. Agnoli. Rome: Pozzi, 1975, pp. 135–149.
22. Wolthuis, O. L., H. de Vroome and R. A. P. Vanwersch. Automatically determined effects of lithium, scopolamine and methamphetamine on motor activity of rats. *Pharmac. Biochem. Behav.* **3:** 515–518, 1975.