Pharmacology Biochemistry & Behavior, Vol. 40, pp. 1–6. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Enhanced Resistance Effect of Piracetam Upon Hypoxia-Induced Impaired Retention of Fixed-Interval Responding in Rats

E. CHLEIDE, J. BRUHWYLER AND M. MERCIER

Department of Psychology, Faculty of Medicine, Namur University, 61 Rue de Bruxelles, 5000 Namur, Belgium (B)

Received 10 December 1990

CHLEIDE, E., J. BRUHWYLER AND M. MERCIER. *Enhanced resistance effect of piracetam upon hypoxia-induced impaired retention of fixed-interval responding in rats.* PHARMACOL BIOCHEM BEHAV **40**(1) 1–6, 1991.—Rats were trained on a fixed-interval schedule of 60 s (FI 60). After stabilization of performance, rats were chronically submitted to hypoxic treatment (3.5% O_2, 10 min) once a day, immediately after the daily FI 60 session. Hypoxia disturbed the retention of FI responding. It was mainly characterized by a decrease in response rate and in pause duration, and by changes in the temporal distribution of responses. Animals receiving piracetam (100 mg/kg, IP) 30 min before each FI session followed by hypoxia were significantly less affected than saline-treated animals. Results are discussed with reference to the effects of hypoxia and piracetam on nonspecific factors and on memory function. It is suggested that the effects of piracetam are due to alleviation of hypoxia-induced memory retrieval deficit rather than to a protection against hypoxic brain cell injury.

Hypoxia Memory Retrieval Fixed-interval schedule Rats Piracetam

VARIOUS lines of experimentation have been employed in the search for drugs which can improve cognitive functions impaired by cerebral deficiencies. This is especially important in the view of the fact that cognitive disorders are widespread in man, mainly in old people. However, the absence of well-defined etiologies for these disease states (e.g., senile dementia, dyslexia, multi-infarct dementia, hyperkinesis, etc.), and the lack of understanding of the detailed neuronal mechanisms involved in cognitive functions can explain the current scarcity of effective treatment for the major cognitive symptoms associated with cognitive decline (1,37).

Piracetam, which is the chef de file of the nootropic drugs (26, 27, 29), has been shown to improve the integrative mechanisms associated with learning and memory in animals (19, 42, 47). Clinical experiments have also demonstrated that piracetam can produce significant improvements in learning and memory in healthy senile patients or patients suffering from brain pathology (14, 38, 46).

Among the strategies employed to study the pharmacological enhancement or protection of learning and memory, hypoxic models have provided a very useful experiment tool allowing the production in laboratory animals of pathological conditions comparable to those which occur in the aged brain (1, 22, 24, 36). Geriatric drugs which have displayed some positive effects on the symptomatology of the aging brain have also proved to be effective in hypoxia models. Numerous reports have demonstrated that piracetam can protect learning and memory against hypoxia in animals [i.e., (25, 28, 40)]. This effect has also been observed in man (14,34).

Mostly these studies have been devoted to the protective effects of piracetam on hypoxia-induced impairment of learning. Only a few studies (if any) have considered the protective effects of the nootrope on hypoxia-induced impairment of a stabilized performance. In a previous experiment (8), we examined the effects of chronic hypoxic treatment on the stabilized performance of rats in a fixed-interval schedule of 60 s (FI 60). After completion of a period of 30 days for the acquisition and stabilization of performance, hypoxia (3.5% O_2 for 10 min) was given once a day, for 3 days, immediately after the FI 60 session. In this way, it could be argued that the storage of the critical information had been completed before the amnestic treatment was applied. The results revealed clear hypoxia-induced impairments of performance as reflected in a sharp drop in response rates and disruption of the temporal distribution of responses.

In the present studies, we employed a similar experimental paradigm. However, the rats received a piracetam or saline injection before each FI 60 session followed by hypoxia. Based on the well-established properties of piracetam for enhancing the resistance of learning against hypoxia, the aim of the present experiments was to elucidate the extend to which piracetam could also protect a stabilized performance against hypoxic brain insult.

METHOD

Animals

Fourteen male Wistar rats, weighing 250–300 g at the beginning of the experiments, were used. They were housed in individual cages and maintained on a 12–12 light/dark cycle.

The ambient temperature was 23 ± 1°C. Two weeks prior to

the start of the experiments, the rats were reduced to and maintained at 80% ad lib body weight.

Apparatus

The apparatus employed consisted of a single lever operant chamber (28 × 19 × 39 cm) with a pressing lever and a food cup for food pellets (Noyes, 45 mg) located 5.5 cm to the right of the lever and 5 cm above the floor. The response lever protruded 3.5 cm out from the right wall, 5 cm above the floor, and was operational under the application of a force of at least 0.3 N. The experimental cubicle was located in a sound-attenuating enclosure, which was illuminated throughout the entire sessions. A camera (ITC-Ikegami) was set at the end of the enclosure to allow indirect observation.

Training-Treatment Procedures

The experiments were usually started at 8:30 a.m. and extended over a period of 7 hours. Each experiment was divided into three parts and commenced at the end of a 2-week food restriction period. On the first day, the rats were placed inside the experimental cubicle and the bar press was shaped in a single session. On the following days, they were first submitted to continuous reinforcement or CRF (50 reinforcements) for 2 sessions followed by one FI 15 s and one FI 30 s session, limited to 25 reinforcements each. For the following 28 days, all subjects were submitted to one daily FI 60 session (FI 60). At the end of each daily session, they were returned to their individual cages and received a supplementary food ration (part 1). For the following 4 daily sessions, groups of 7 animals were assigned to two different kinds of treatment conditions. The animals of one group received a saline injection at 30 min before the FI 60 sessions (Sal-H group), and the other group received an injection of piracetam at 30 min before the FI 60 session (Pir-H group). The dose of piracetam (100 mg/kg) and time of injection were selected in the present experiments on the basis of animal studies. The rats of both groups were exposed to hypoxia immediately after each daily session and were then returned to their home cage (part 2). From sessions 33 to 39 (part 3), the two groups of rats were subjected to a treatment similar to that in part 1. The animals were submitted to a daily FI 60 session without pre- or postsession treatment.

Hypoxia

The equipment used to induce hypoxia was similar to that described previously (8). It consisted basically of a Plexiglas cage (28 × 20 × 14 cm), into which pure nitrogen and oxygen were delivered, and a fan served to homogenize the gas content. The animals were subjected to hypoxia by being exposed to 3.5% oxygen for 10 min, after which they were returned to their home cage. The composition of the air in the hypoxia cage was monitored continuously with an OM-15 Oxygen Monitor (Sensor Medics).

Data Presentation and Statistical Analysis

Three dependent variables were analyzed: the postreinforcement pause duration, the overall response rate, and the number of late responses (i.e., those responses made after more than 70 s). Group differences were evaluated using a two-factor fixed design analysis of variance for repeated measures (16). The analysis was performed separately for the three parts of the experiments: acquisition of the task (part 1), the 4 sessions involving hypoxia, with or without piracetam (part 2), and the six FI 60 sessions without pre- or postsession treatment (part 3). The temporal distribution of responses (TDR) in successive segments of the schedule were available for every session. A fourth variable was also analyzed by ANOVA, viz., the number of fecal pellets produced by the subjects during each FI 60 session.

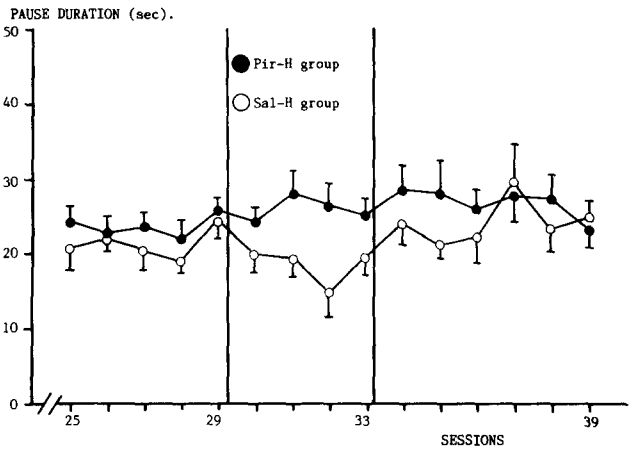

FIG. 1. Pause duration for the 5 sessions of the stabilized performance (sessions 25 to 29), the 4 sessions consecutive to daily hypoxia (sessions 30 to 33), and the 6 sessions without drug or hypoxic treatment. Rats received a saline or piracetam injection 30 min before sessions 29 to 32. Mean values are shown with S.E. mean indicated by vertical bars.

RESULTS

In both groups of rats, the performance was stabilized from the 15th FI 60 session. The two groups of rats did not differ significantly in their postreinforcement pause duration, $F(1,50) = 1.27$, and number of late responses, $F(1,50) < 1$, for the final five FI 60 sessions of the stabilized performance (Figs. 1 and 2). A significant difference was found between the two groups in terms of the response rate, $F(1,50) = 7.02$, $p < 0.05$. However, the analysis of variance showed that the three parameters did not vary significantly ($F < 1$ in all cases) throughout the final 5 sessions of the stabilized performance (Figs. 1–3).

The TDR (Fig. 4) and the number of late responses were similar in both groups of rats for the FI 60 session consecutive to the first saline or piracetam injection (Fig. 4, day 29), indicating that the drug treatment did not modify the stabilized FI 60 performance. On the other hand, a positive effect by piracetam appeared during the 4 sessions consecutive to hypoxia (day 30 to 33). For these 4 sessions, the two groups of rats differed significantly in their pause duration, $F(1,40) = 4.1$, $p < 0.05$, and number of late responses, $F(1,40) = 12.3$, $p < 0.01$. The TDR of the Sal-H group exhibited marked impairment consisting of a drop in the number of responses provided at the end of the interval. A slight increase was also observed in the early responses (Fig. 4). The effects of hypoxia were minimized in the Pir-H group, but the protection provided by piracetam was partial. Indeed, the response rate was decreased in both groups. Despite the fact that this parameter was significantly different between the two groups, $F(1,40) = 6.9$, $p < 0.05$, the curves in Fig. 3 demonstrate that the hypoxia-induced decrease was similar for the two groups. It is interesting to note, however, that this decrease in response rate was not traduced by modification of the pause duration in the Pir-H group. Moreover, both the TDR and

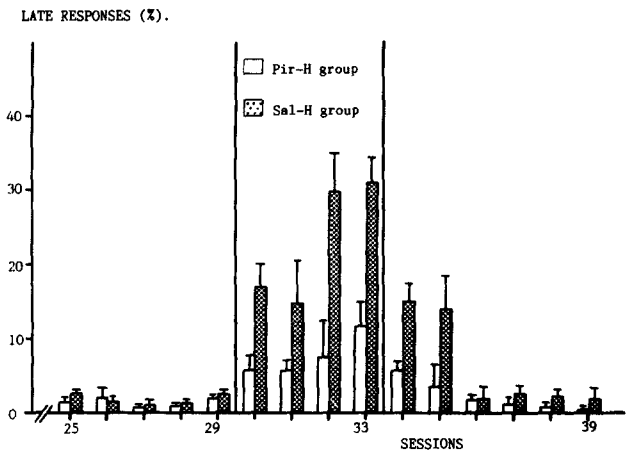

FIG. 2. Evolution of the late responses for the 5 sessions of the stabilized performance (sessions 25 to 29), the 4 sessions consecutive to daily hypoxia (sessions 30 to 33), and the 6 sessions without drug or hypoxic treatment. Rats received a saline or piracetam injection 30 min before sessions 29 to 32. Mean values are shown with s.e. mean indicated by vertical bars.

number of late responses were clearly less affected by hypoxia, as compared to those in the Sal-H group. Analysis of variance for the interaction between treatment and days revealed that the effect of the treatment was the same for the pause duration, response rate and number of late responses throughout the 4 days since the interaction was not significant.

During the third part of the experiments, we observed a recovery of performance. This recovery was more or less rapid depending on the parameter. The pause duration returned to the baseline value within one session, while the response rate and the number of late responses failed to return to the baseline value before at least the third session. Analysis of variance revealed that the only significant difference between the Sal-H group and Pir-H group was limited to the response rate, $F(1,60)=6.2$, $p<0.05$. A final analysis concerning the number of defecations

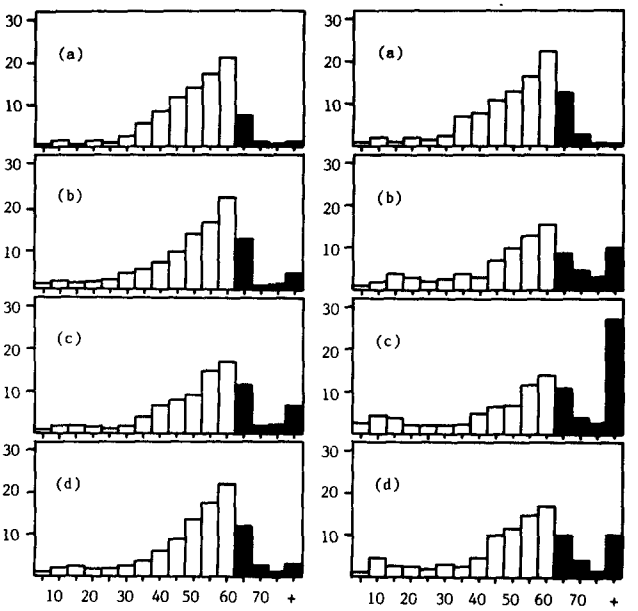

FIG. 4. Temporal distribution of responses for piracetam- (left) and saline- (right) treated group for the first FI session followed by hypoxia (a, session 29), the first FI session consecutive to hypoxia (b, session 30), the fourth FI session consecutive to hypoxia (c, session 33), and the first FI session scheduled after stopping drug and hypoxic treatment (d, session 34).

(Fig. 5) yielded no significant differences ($p<1$) between the two groups of rats in the three parts of the experiments.

DISCUSSION

The present study shows that piracetam can markedly attenuate the hypoxia-induced deficits of a stabilized performance in an FI schedule. The implication of nonspecific factors (i.e., a

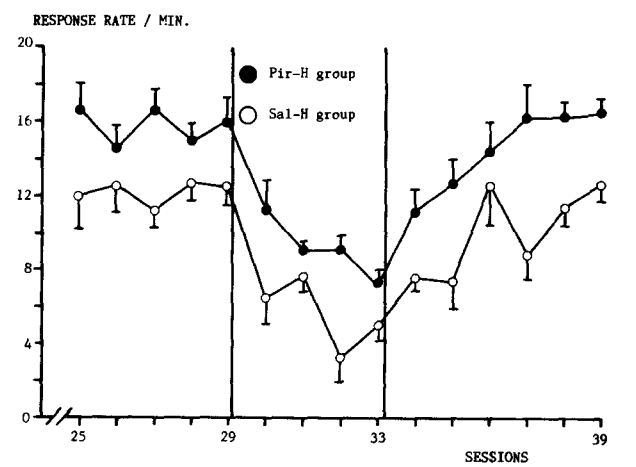

FIG. 3. Response rate for the 5 sessions of the stabilized performance (sessions 25 to 29), the 4 sessions consecutive to daily hypoxia (sessions 30 to 33), and the 6 sessions without drug or hypoxic treatment. Rats received a saline or piracetam injection 30 min before sessions 29 to 32. Mean values are shown with s.e. mean indicated by vertical bars.

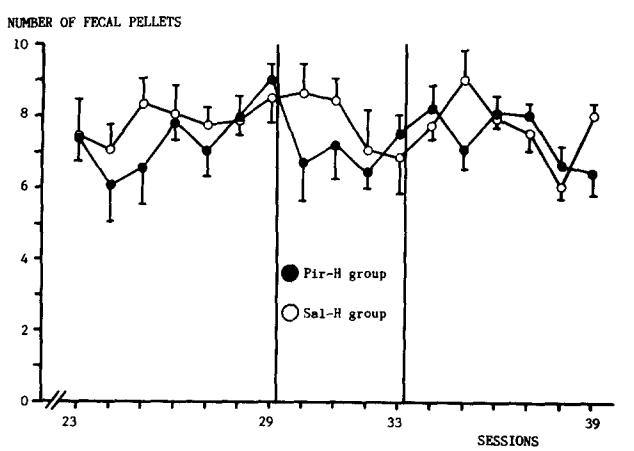

FIG. 5. Evolution of the number of fecal pellets produced by the rats during the 7 sessions of the stabilized performance (session 23 to 29), the 4 sessions consecutive to daily hypoxia (sessions 30 to 33), and the 6 sessions without drug or hypoxic treatment. Rats received a saline or piracetam injection 30 min before sessions 29 to 33. Mean values are shown with s.e. mean indicated by vertical bars.

hypoxia-induced decrease of motor activity, stress, anhedonia, etc.) in explaining the effects of hypoxia has been extensively discussed previously in a study employing a similar procedure (8). It was concluded that the impairments of performance in the FI schedule might be due to retrieval failure from long-term memory or brain cell damage induced by hypoxia. The aim of the present study is to explain the resistance provided by piracetam against the effects of hypoxic treatment on the FI performance.

Can the protective action of piracetam be accounted for by a stimulation of motor activity, an enhanced motivation or an anxiolytic activity?

Alterations in motor performance following hypoxia would indicate that the protective effects of piracetam might be due to the drug acting at the motor level. However, it has been shown that hypoxia failed to influence the activity of rats at 24 hours after treatment (8, 17, 20, 42). Moreover, piracetam, when given alone, exerted no stimulant effect at the behavioral level (19, 26, 27, 35, 47). Neither did it influence the early postnatal hypoxia-induced increase of motor activity in rats (31). In the present study, no increase in response rate was observed in the first FI session, at 30 min after the first piracetam injection (Fig. 3, day 29). However, this parameter was significantly depressed at 24 hours after hypoxia in the saline group as well as in the piracetam-treated group. Taken together, these data support the view that piracetam exerted its antihypoxic protective action by a mechanism different from stimulation of motor activity.

It could be conjectured that piracetam might enhance motivation or arousal. Nevertheless, this suggestion, however attractive it may be, appears unlikely mainly for the following 2 reasons. First, it has been shown that the disruption of performance observed 24 hours after hypoxia was not the mere consequence of motivational modification (8,17). On the other hand, in view of the fact that motor activity is not modified either by piracetam (19, 26, 27, 35, 47) or by hypoxic treatment given 24 hours previously (8, 17, 20, 42), any piracetam-induced increase of motivation should lead to an increase in response rate for the FI 60 consecutive to hypoxia. The present results (Fig. 3) showed that this parameter was decreased in both groups of rats. This explanation is in agreement with a study in which piracetam improved the retention of a continuously reinforced bar-press response for water reward in rats. Piracetam did not induce any modulation of activity or motivation but rather facilitated the retrieval process (42).

The validity of an explanation involving an anxiolytic activity of piracetam also seems unlikely. Hypoxia has been shown to constitute a nonaversive stimulus, i.e., one that failed to produce anxiety-like behavior (8,21). It is also worthy to note that in the present study the Skinner cage and hypoxia cage were located in different rooms. Hypoxia-induced conditioned fear means that hypoxia induces a strong emotional reaction which would be revived when the animal was replaced in the Skinner cage. However, we did not observe any behavior traducing stress in rats during the four FI sessions consecutive to hypoxia, and hypoxia did not induce any change in the number of fecal pellets, a parameter widely employed as a sign of anxiety.

Based on the data in the literature and those obtained in the present study, the action of piracetam could apparently be situated at the level of mnesic retrieval function, which may be disrupted by hypoxia. This proposition derives from the fact that performance was definitely stored before the onset of the amnestic treatment. Therefore, hypoxia cannot act upon the fixation process, in contrast to the situation where the amnestic treatment is carried out immediately after the learning session. Under such circumstances, one can assume that the impairment of the memory acquired prior to the administration of hypoxia must be essentially an impairment of the retrieval process (2, 13, 23).

Hypoxia has been repeatedly reported to induce retrieval failure (2, 17, 41). At the same time, nootropics were shown to facilitate the retrieval process (42), and to be active against memory retrieval deficits induced by different treatments such as electroconvulsive shocks, cycloheximide, scopolamine and hypoxia (3, 15, 18, 43). There is, however, a lack of data concerning the mechanisms which underlie the effect of both hypoxia and piracetam on the retrieval function. In the present case, the effects of piracetam can be explained either in terms of structural protection or in terms of functional enhancement.

According to the first proposition, piracetam would protect brain cells against hypoxia-induced severe long-lasting structural alterations. It is well known that brain cells, especially of the neocortex area (6,45), are extremely sensitive to changes in the oxygen concentration in the blood and that severe interruption of oxygen inflow will lead to irreversible cerebral damage. Research in the last decade has lead to the identification of glutamate as a principal factor triggering cerebral hypoxic-ischemic injury mechanisms. Different laboratories have shown that severe hypoxia and ischemia give rise to a large and rapid increase in glutamate release from excitatory terminals, allowing glutamate to reach neurotoxic concentrations [for reviews, see, for example, (11,39)]. It could be postulated that the performance of the Pir-H group results from the protection afforded by piracetam against hypoxia-induced cell death. This explanation is not supported by results obtained previously by the brain microdialysis technique. In a study examining the effects of hypoxia on the release of amino acids in rats subjected to either 10 or 5% O_2 for 1 h, no significant increase in glutamate release was recorded except during the last 15 min of hypoxia at 5% O_2 (9). On the other hand, important increases in glutamate levels were observed from the first min of anoxia (5,9) or ischemia (4,30). Moreover, we have demonstrated that the striatal and hippocampal glutamate concentrations were not significantly increased in rats sacrificed immediately, or at 10, 30 min or 24 hours after hypoxic treatment (3.5% O_2 for 10 min) (10). These data are in agreement with the view that the brain cell death induced by brief oxygen deprivation occurs only under extreme conditions; that is, anoxia or ischemia. When using severe hypoxia (1 to 5% O_2). It has been shown that prolonged hypoxia (several hours) are requested for inducing morphologic evidence of cellular dysfunction (32,33). It seems rather unlikely, therefore, that the performance of the sal-H group can be explained by hypoxia-induced brain cell death.

These observations led us to investigate the second proposition, namely the influence of hypoxia and piracetam on memory retrieval function. As pointed out by Sara (43), the behavioral organization involved in memory retrieval necessarily implies an integration of the incoming information available in the environment, endogenous information relating to homeostasis, and previously acquired information represented in the nervous system of the organism. It is on that integrative activity which hypoxia and piracetam would act. This explanation is corroborated, at the theoretical level, by the analysis made by Sarter (44) concerning the modes of action of nootropics. According to the ideal theoretical curve, the application of a drug facilitating retrieval must be carried out after the acquisition period because the treatment may function like a "rehearsal." At the experimental level, the results of previous studies have revealed positive effects of nootropics on memory retrieval deficits induced by amnestic treatments of different types (3, 15, 18, 43). For example, Sara (43) and Barzaghi et al. (3) found that nootropic agents could reverse the amnesia induced by scopolamine or electroconvulsive shocks. In these two studies, the amnestic treatment was given immedi-

ately after a one-trial avoidance task, and the drugs were injected 30 min prior to retention testing. De Noble et al. (18) also demonstrated that vinpocetine and aniracetam were effective in preventing hypoxia-induced retrieval deficits, when administered orally 40 min before the start of the first hypoxic episode. In these last experiments as well as in the present ones, piracetam appeared to act not through a protective action but rather by facilitating the integrative activity of memory retrieval, which is disturbed by the amnestic treatment. It is worth pointing out that the term "integrative activity" covers both the mnesic aspects and the temporal aspects of the FI 60 schedule. It is difficult here to distinguish further whether hypoxia and piracetam act only on the memory retrieval process or on the time estimation process, since these two types of processes occur in a highly interactive manner during the FI 60 session. This point has been clearly emphasized in the conclusions of Campbell (7) based on a study in which rats aged from 6 to 26 months were trained for a period of one week on an FI 60 schedule. After a 16-day retention delay, the old rats appeared to have forgotten the precise temporal characteristics of the schedule while retaining the basic press response itself. These findings can be explained by a disruption in the retrieval process; that is, rats do not forget the bar press response since the experimental setting provides a large number of stimuli which could act as retrieval cues. However, the Skinner cage provides no information regarding the appropriate pattern of response distribution (7). The present results demonstrated that the bar press response was also retained by the Sal-H rats but they appeared to forget the precise moment at which the reinforcement became available. It can be argued that hypoxia and piracetam affect the cerebral process involved in the recall of the optimal distribution of responses.

That above explanation is supported by reports of retrieval facilitation by piracetam. The large number of studies which have demonstrated the effects of hypoxia and piracetam on memory function contrasts with a lack of data relating the effects of these two agents in terms of the time estimation process. The information available in the literature and that obtained in the present experiments lend support to the previous proposal that piracetam may facilitate the integrative activity of memory retrieval. Experiments are now in progress to determine the extent to which such an effect involves an action on the endogenous temporal control.

ACKNOWLEDGEMENTS

The authors are grateful to UCB S.A. (Belgium) for its generous gift of piracetam. Mr. J. P. Peters and V. Mineur are gratefully acknowledged for their technical assistance. This work was in part financially supported by grant 890962 to E.C. from the Japanese Ministry of Education, Science and Culture.

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