

A continuous recording of two biological functions of circadian rhythmicity (drinking and motor activity) was carried out in four groups of rats aged 3 months (young animals), 6 months (adult animals), 18 months (presenescent animals) and 24 months (old animals).

The rats were bred in groups under standard conditions (LD 12:12, T°22°C) and provided with food and water ad lib. They were never submitted to modifications of temporal indicators (atypical Zeitgeber), which could generate an external disturbance of the circadian rhythm of the two studied functions.

During the experiment, the animals were left in individual cages for 10 consecutive days and then transported daily, on a trolley, for 5 consecutive days. The effect of isolation and transport was measured by the recording of the evolution of the body weight and of the drinking and motor activity rhythms. The higher weight loss and the most important changes in the ultradian components of these rhythms were observed in the two older groups; this could suggest the existence of a different reactivity to disturbance and of an increasing vulnerability of the circadian system during aging.

The similarity between these results observed in old rats submitted to disturbances, with those observed in young adult rats, submitted at an early age (1 to 18 days) to atypical Zeitgeber (Knaepen and Weyers, 1988, *Physiol. Behav.*, 44: 763-767), suggests that early manipulation of the circadian system could provide a paradigm of the accelerated aging in animals.

Amineptine and response timing in the rat

H. Lejeune, I. Hermans, E. Mocaër¹, M.J. Rettori¹ and M. Richelle

Experimental Psychology Laboratory of the University of Liège, Belgium, and ¹ Institut de Recherches Internationales Servier, Paris, France

The operant Fixed Interval (FI), Differential Reinforcement of Low rate (DRL) and duration discrimination schedules (5) were used to assess the effect of the antidepressant drug amineptine (2, 4) on internal clock mechanisms. Subjects were groups of 10 adult male albino rats (Wistar). Injections (i.p.) were made in each case after stabilization of performance, 20 min before the beginning of the daily session. Experiment 1 tested single doses of 1, 5, 10 and 20 mg/kg on response rate variables and response timing in FI and DRL. Experiment 2 explored the effects of the chronic injection of a dose of 10 mg/kg on FI, DRL and duration discrimination behavior. Experiment 3 was aimed at testing the effect of a chronically injected low dose of the drug (1 mg/kg) in FI and DRL. Taken together, results from Experiment 1 show a dose-dependent effect of the drug on response rate and response timing: response rates increased significantly, whereas response timing was significantly impaired. However, the lowest dose of the drug (1 mg/kg) induced a non-significant trend towards a decrease in response rates and an improvement of the temporal regulation of behavior. Experiment 2 replicated findings from Experiment 1. Furthermore, the accuracy of temporal discrimination between auditory stimuli lasting respectively for 2 and 8 s was not affected by the chronically injected dose of 10 mg/kg.

Experiment 3 partially replicated findings from Experiment 1. Nevertheless, as in Experiment 1, trends did not reach statistical significance.

Results collected over the successive experiments show that amineptine at doses of 5, 10 and 20 mg/kg exerts an aspecific stimulation on operant responding in FI and DRL, without specifically altering internal clock mechanisms (duration discrimination). Impairment of response timing in FI and DRL is most probably a by-product of increased motor activity (1). Results also indicate that the 10 mg/kg dose does not induce behavioral tolerance (3), sensitization or dependence as assessed from operant responding (other behaviors were not recorded). The absence of significant effects of the 1 mg/kg injections precludes the use of this dose of the drug as a cognitive enhancer, within the limits of the type of task described here. Finally, results suggest that improvements in temporal 'awareness' or 'anticipation' observed in depressed patients treated with the drug might not be bound to a specific effect of the drug on timing mechanisms, but rather result from its overall aspecific stimulating effects.

References

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Aversive conditioning to contextual and punctuate stimuli

J.H.R. Maes and J.M.H. Vossen

Comparative & Physiological Psychology, University of Nijmegen, P.O. Box 9104, 6500 HE Nijmegen, The Netherlands

In each of four classical conditioning experiments, rats were used as subjects and freezing was the index of conditioned responding. The first experiment examined the course of freezing to contextual stimuli as a response to the delivery of a single, unsignalled, electric footshock. In three groups of rats, the time of shock presentation was manipulated while the total amount of time spent in the shock context was equated among groups. One group received the shock early in the session. A second group was shocked at the middle, and a third group received the shock at the end of the session. An additional control group was included that did not receive a shock. Relative to the early-shock group, the other two shock groups demonstrated a retarded onset of freezing after the shock delivery. During a