J. Pharm. Pharmacol. 1993, 45: 137–138
Communicated January 2, 1992

COMMUNICATIONS

The effect of reserpine and stress on feeding behaviour in the light and dark phases of the diurnal cycle in rats

Z. GORKA, P. ADAMIK, *Institute of Pharmacology, Polish Academy of Sciences, Smetna 12, 31–343 Krakow, Poland*

Abstract—The effect of reserpine (2·5 mg kg^{-1} subcutaneously) and stress (3 h restraint) on food and water consumption and body weight change in the light and dark phases of the diurnal cycle in rats was investigated. Reserpine increased water intake and body weight loss in the light phase (250 and 180% of the control, respectively). In the dark phase the reserpinized rats consumed less food and water (20 and 30% of the control, respectively) and body weight gain was reversed (−250% of the control). After stress, rats consumed more food and water (200 and 500% of the control, respectively) and their body weight loss was diminished (60% of the control) in the light phase. In the dark phase the consumption of food and water in the stressed rats was diminished (80 and 85% of the control, respectively) without any change in body weight gain. The dark/light phase ratio for food consumption, water intake and body weight change (gain/loss) was highly statistically significant in the stressed and reserpine-treated rats. The results indicate that evaluation of behaviour in animal models should be carried out during both phases of the diurnal cycle.

Antidepressant drugs were introduced into the treatment of depressed patients more than 30 years ago (Crane 1957; Kuhn 1958). Since then succeeding generations of these drugs have been used, yet the mechanism of their therapeutic action is not clear. Pharmacological effects occur almost immediately after administration of a single dose, whereas therapeutic efficacy is demonstrated in depressed patients only after two or three weeks of treatment (Oswald et al 1972); mood in depressed subjects, but not in healthy people is improved. The majority of pharmacological tests for screening for antidepressant properties (see Maj et al 1984) are based on behavioural studies of normal rodents during the day-time, that is, in their period of inactivity and any testing is confounded by disturbance of the animal's sleep. In addition, most studies of animal models of depression (see Willner 1984) have been carried out in the light phase of the day only. Since rats are mostly active during the dark phase and there is evidence for light/dark phase differences in the effects of drugs (Lemmer 1984; Redfern et al 1985), it seems that a more promising methodological approach in pharmacological studies of putative antidepressants in rodents is that which takes into consideration both factors; that is, the tested animals should be 'depressed' ones and the tests should be performed at all phases of the light/dark regimen.

In the present experiments, we investigated whether factors which induce depressive-like behaviours in rodents, such as reserpine and restraint stress (Costa et al 1960; Anisman & Zacharko 1982), influence prominent physiological features of behaviour of rats (feeding behaviour and body weight gain) to the same extent in both light and dark phases.

Materials and methods

Experiments were carried out on male Wistar (IF PAN) rats, 260–280 g, with free access to granulated food (LSM Motycz) and tap water. The rats were individually housed in polycarbonate cages (Macrolon, 36 × 22 × 20 cm) at an ambient temperature of 22 ± 0·5°C and on a 12 h light-dark schedule (lights on between 0700–1900 h) for at least one week before the start of the experiment. The intensity of illumination was 200 lux in the light phase and < 0·1 lux the dark phase. Animals were randomly divided into control and treatment groups. Each group consisted of ten animals and was tested in one half of the light/dark cycle only. At the beginning of each phase the rats were weighed and given reserpine or subjected to the restraint stress. At the end of each phase the amount of food and of water consumed was assessed by weight measurements of the food and water containers. Spillage of food and water was minimized. In addition, the rats were weighed again and their body weight gain was assessed on the basis of the difference between the before and after measurements. Reserpine (Rausedyl, Gedeon Richter, Budapest) was administered in a dose of 2·5 mg kg^{-1} subcutaneously in a volume of 2 mL kg^{-1} of Water for Injection. For restraint stress, rats were restrained in acrylic restrainers (20 × 6 × 6 cm), with an adjustable tail plate, for 3 h. During this period the whole animal was restrained without any access to food and water. Control groups received the same volume of the solvent or were left undisturbed in their home cages, respectively. Results (in g) were calculated as the means ± s.e.m. of the group. The statistical significance was assessed by a one-way analysis of variance and Dunnett's *t*-test.

Correspondence: Z. Gorka, Institute of Pharmacology, Polish Academy of Sciences, Smetna 12, 31–343 Krakow, Poland.

Results

Reserpine did not change food consumption in comparison with the control group, and increased water intake (6·0 ± 0·7 compared with control 2·4 ± 0·3 g) and body weight loss (−18·2 ± 1·3 compared with control −10·9 ± 1·0 g) in the light phase. In the dark phase the reserpinized rats consumed less food (3·9 ± 0·9 compared with control 25·0 ± 0·5 g) and water (10·5 ± 0·7 compared with control 36·4 ± 2·2 g). Rather than body weight gain, which is observed in the control rats in this phase, body weight loss (−17·8 ± 1·0 compared with control 12·2 ± 1 g) was seen in the reserpine-treated rats (Fig. 1a).

After restraint stress, rats consumed more food (5·2 ± 0·6 compared with control 2·5 ± 0·4 g) and water (11·4 ± 0·5 compared with control 2·2 ± 0·3 g) than non-stressed animals and diminished their body weight loss (−6·2 ± 2·2 compared with control −10·8 ± 1·0 g) in the light phase. In the dark phase the consumption of food (21·0 ± 1·1 compared with control 25·3 ± 0·5 g) and water (31·0 ± 2·3 compared with control 36·2 ± 2·0 g) in the stressed rats was diminished without any change in body weight gain (Fig. 1b).

The dark/light phase ratio for food consumption, water intake and body weight change (gain/loss) was highly statistically significant in the stressed and reserpine-treated rats (Fig. 2).

Discussion

The present study confirms that food and water consumption in

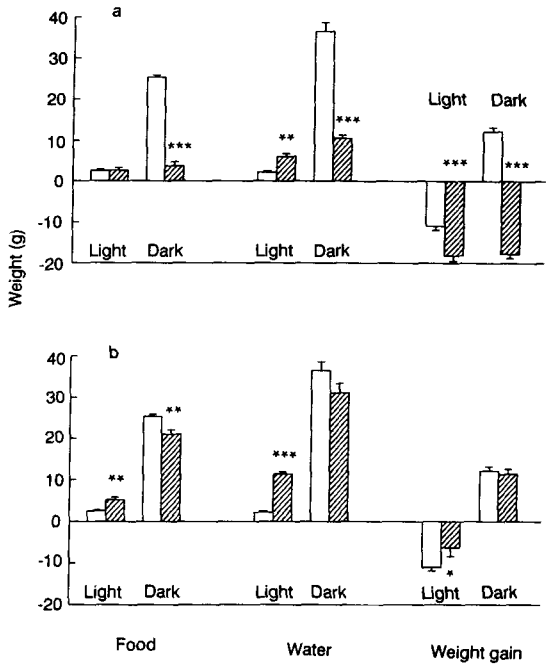

FIG. 1. Food consumption, water intake and body weight gain in rats after (a) reserpine (2·5 mg kg^{-1}, s.c., ■) and (b) restraint stress (3 h, ▨) in the light and dark phases. Control, □. The bars represent the mean values (g)±s.e.m. for ten rats. $*P<0·05$, $**P<0·01$, $***P<0·001$ compared with control (Dunnett's t-test).

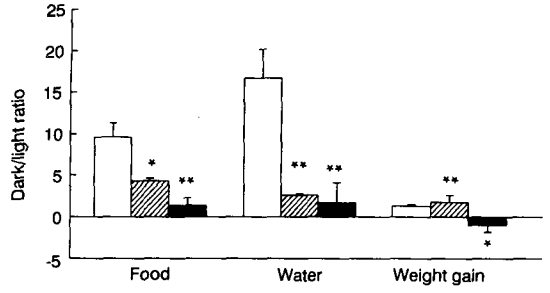

FIG. 2. Dark/light phase ratio for food consumption, water intake and body weight change (gain/loss) in the control (□), stressed (▨) and reserpine-treated (■) rats. $*P<0·01$, $**P<0·001$ compared with control, analysis of variance followed by Dunnett's t-test.

normal rats differs between the light and dark phases of the rat's daily cycle and predominantly occurs in the dark or active phase (Zucker 1971; Spiteri 1982). Moreover, phase differences were observed also in body weight. The consumption of food and water during the light phase is insufficient to keep body weight at a steady level and at the end of this phase body weight is lower than at the beginning. In the dark phase, by contrast, body weight is gained and exceeds body weight loss in the light phase. It has been previously shown that the energy value of the food consumed at night is roughly 50% greater than the energy output during this time, while in the daytime it is about 50% smaller (Le Magnen 1981).

The temporal regulation and rhythmicity of feeding and drinking may be related to the diurnal fluctuations of various neurotransmitters and hormones (noradrenaline, adrenaline, dopamine, 5-hydroxytryptamine, certain peptides and γ-amino butyric acid), their enzymes, metabolites and receptors (Leibowitz 1981; Krauchi et al 1984; Jhanwar-Uniyal et al 1986; McLaughlin et al 1987; Noskovic et al 1989).

The main finding of our study is that the effects of reserpine and restraint stress on rat feeding behaviour in the light phase differ quantitatively and qualitatively from those observed in the dark phase. Moreover, restraint stress seems to have far less effect upon the behaviour than does reserpine.

It is evident that evaluation of the behavioural effects of both stimuli performed on the basis of studies carried out in the light phase only (as is performed in the majority of pharmacological experiments), is incomplete. Conclusions based on the results of experiments carried out in the light phase may not be valid for the dark phase.

References

Anisman, H. A., Zacharko, R. M. (1982) Depression: the predisposing influence of stress. Behav. Brain Sci. 5: 89–137

Costa, E., Garattini, S., Valzelli, L. (1960) Interactions between reserpine, chlorpromazine and imipramine. Experientia 16: 461–463

Crane, G. E. (1957) Iproniazid (Marsilid) phosphate, a therapeutic agent for mental disorders and debilitating diseases. Psychiatr. Res. Rep. 8: 142–152

Jhanwar-Uniyal, M., Roland, C. R., Leibowitz, S. F. (1986) Diurnal rhythm of alpha2-noradrenergic receptors in the paraventricular nucleus and other brain areas: relation to circulating corticosterone and feeding behaviour. Life Sci. 38: 473–482

Krauchi, K., Wirz-Justice, A., Morimasa, T., Willener, R., Feer, H. (1984) Hypothalamic alpha2- and beta-adrenoceptor rhythms are correlated with circadian feeding: evidence from chronic methamphetamine treatment and withdrawal. Brain Res. 321: 83–90

Kuhn, R. (1958) The treatment of depressive states with G22355 (imipramine hydrochloride). Am. J. Psychiatr. 115: 459–464

Leibowitz, S. F. (1981) Brain catecholamine projections: their function in control of spontaneous and drug-induced changes in feeding behavior, appetite, and body weight. Psychopharmacol. Bull. 17: 59–66

Le Magnen, J. (1981) The metabolic basis of dual periodicity of feeding. Behav. Brain Sci. 4: 561–607

Lemmer, B. (1984) Chronopharmakologie—Tagesrhythmen und Arzneimittelwirkung. Wiss. Verlagsgesellschaft, Stuttgart

Maj, J., Przegalinski, E., Mogilnicka, E. (1984) Hypotheses concerning the mechanism of action of antidepressant drugs. Rev. Physiol. Biochem. Pharmacol. 100: 1–74

McLaughlin, C. L., Baile, C. A., Della-Fera, M. A. (1987) Circadian rhythm of feeding induced changes in hypothalamic Met-enkephalin concentrations. Physiol. Behav. 41: 465–469

Noskovic, P., Kuchar, S., Mozes, S., Koppel, J. (1989) Circadian changes in the RNA content of rat hypothalamic nuclei in relation to food intake. Physiol. Bohemoslov. 38: 127–133

Oswald, I., Brezinova, V., Dunleavy, D. L. F. (1972) On the slowness of action of tricyclic antidepressant drugs. Br. J. Psychiatr. 120: 673–677

Redfern, P. H., Campbell, I. C., Davies, J. A., Martin, K. F. (1985) Circadian Rhythms in the Central Nervous System. VCH, Weinheim

Spiteri, N. J. (1982) Circadian pattern of feeding, drinking and activity during diurnal food access in rats. Physiol. Behav. 28: 139–147

Willner, P. (1984) The validity of animal models of depression. Psychopharmacology 83: 1–16

Zucker, I. (1971) Light-dark rhythms in rat eating and drinking behaviour. Physiol. Behav. 6: 115–126