well correlated in time with the locomotor stimulation, sniffing and gnawing. It seems, therefore, that quipazine may interact with dopamine receptors.

Quipazine also counteracted reserpine-induced catalepsy (Fig. 1). This confirms the findings of Rodriguez & Pardo (1971) about the anti-reserpine action of quipazine.

We would like to thank Dr. D. A. Stauffer (Miles Laboratories) for his generous gift of quipazine.

Institute of Pharmacology,   M. GRABOWSKA
Polish Academy of Science,   L. ANTKIEWICZ
Cracow,   J. MICHALUK
Poland.

July 13, 1973

REFERENCES

DELINI-STULA, A. & MORPURGO, C. (1968). *Int. J. Neuropharmac.*, **7**, 391–394.
ERNST, A. M. (1969). *Acta physiol. pharmacol. néerl.*, **15**, 141–154.
HADZOVIC, S. & ERNST, A. M. (1969). *Eur. J. Pharmac.*, **6**, 90–95.
HONG, E., SANCILLO, L. F. & VARGAS, R. (1969). *Ibid.*, **6**, 274–280.
RODRIGUEZ, R. (1972). *Life Sci.*, **11**, 535–544.
RODRIGUEZ, R. & PARDO, E. G. (1971). *Psychopharmacologia*, **21**, 89–100.

Daily susceptibility variations to the morphine-induced hyperactivity of rats

Morphine-treated mice display quantitative variations of susceptibility to the analgesic response at different times of the day (Morris & Lutsch, 1969; Lutsch & Morris, 1972). Susceptibility to methadone has also been found to vary as a function of the time of administration in the rat (Lenox & Frazier, 1972).

In an earlier investigation (Ayhan & Randrup, 1973a,b), we observed that behavioural excitant effects of morphine were less pronounced when the drug was injected in the morning. We have now investigated this phenomenon more rigorously.

Male Wistar rats, 200–250 g, were kept in individual cages (21 × 27 × 16 cm) at 21–24° in the dark except for a period of light from 08.30 to 18.30 h. Morphine (2 mg kg⁻¹) was injected intraperitoneally after 5 h of light (13.30 h), at the end of the light period (18.30 h), after 5 h of darkness (23.30 h) and at the end of the darkness (08.30 h). Control rats received saline at the same times.

All rats were observed for 90 min following the injections. Locomotion was assessed as the number of times the rat crossed the midline of the cage, and rearing by the number of the times the rat stood on its hindlegs. The data were analysed statistically by Student's *t*-test (Snedecor, 1956).

As shown in Fig. 1, there was a significant increase in the activity produced by morphine during the course of the day from 08.30 to 23.30 h. The mean locomotor and rearing activities were greatest at the middle of the dark period with the lowest point at the end of the darkness.

The time-response relation of activities was different for morphine and saline. Fig. 2 shows that, after the injection at 08.30 h, morphine produced a significant depression during the first 30 min but thereafter an increase in the locomotor activity up to the 90 min, as did the injections of drug at 13.30, 18.30 and 23.30 h. The locomotor activity of saline-treated rats was the reverse.

There is strong evidence that the central catecholamines, dopamine and noradrenaline, are involved in the control of motor activity in the rats (van Rossum, 1970; Svensson & Waldeck, 1970; Svensson, 1971). But available data indicate that the
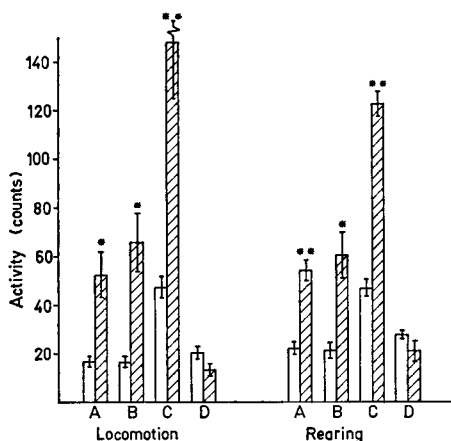
FIG. 1. Effect of morphine on the locomotor and rearing activity of rats at different times of the day. Open columns, saline 1 ml kg^{-1}; hatched columns, morphine 2 mg kg^{-1} n = 8 for each group. Vertical lines on the bars refer to s.e. of mean   A. Injections at 13.30 h.   B. Injections at 18.30 h.   C. Injections at 23.30 h. D. Injections at 08.30 h.

* P <0·01; ** P <0·0005 (compared with respective saline controls).

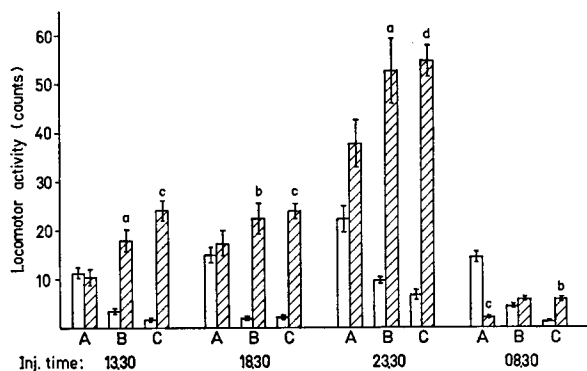
FIG. 2. The time-response relations of locomotor activity of rats induced by morphine. Open columns, saline 1 ml kg^{-1}; hatched columns, morphine 2 mg kg^{-1} n = 8 for each group. Vertical lines on the bars refer to s.e. of mean. A. 1–30 min after injections. B. 31–60 min after injections. C. 61–90 min after injections. ᵃ P <0·0125, ᵇ P <0·01, ᶜ P <0·0025, ᵈ P <0·0005 (compared with respective saline controls).

concentration of noradrenaline shows some variations over 24 h in certain parts of the rat brain (Manshardt & Wurtman, 1968; Friedman & Walker, 1968; Scheving, Harrison & others, 1968) and of cats (Reis & Wurtman, 1968). These regions include the upper portion of the cervical cord and especially certain regions of hypothalamus. In the rat hypothalamus two circadian rhythms of noradrenaline have been identified, one in the anterior hypothalamus, the other in the posterior hypothalamus; both have a peak in the middle of the daily dark period (Manshardt & Wurtman, 1968). The increased concentration of noradrenaline during the dark period could be caused by enhanced synthesis, decreased release or a decreased metabolism (Wurtman, Axelrod & others, 1967; Zigmond & Wurtman, 1970).

Since motor activity of rats also shows diurnal cycles, it is possible that cyclic changes in brain noradrenaline are involved in generating the rhythm of this function. In addition, such cyclic variations of noradrenaline have been shown to result in parallel alterations in the physiologic responses to drugs which act via interaction with catecholamines in the brain (Pauly & Scheving, 1964; Scheving & others, 1968).

The present results demonstrate that susceptibility to morphine as measured by the stimulation of motor activity changed significantly according to time of administration. Previous studies have shown that stimulation of the behaviour of rats by small, acute doses of morphine is closely related to the brain catecholamines (Davis, Babbini & Khalsa, 1972; Ayhan & Randrup, 1973a) and that brain noradrenaline probably plays a more important role than dopamine in the mediation of this behavioural stimulation (Ayhan & Randrup, 1973a,b). Hence, it would seem possible that the changes of the susceptibility to the behavioural stimulant action of morphine might be due to the rhythmic fluctuations of noradrenaline concentration in some regions of the rat brain.

A significant correlation between the presence of a daily rhythm of noradrenaline in any region of the cat brain and the susceptibility of that region to the noradrenaline-depleting action of morphine was reported by Reis, Rifkin & Corvelli (1969). The response of the cat to morphine is behavioural excitation and this excitation is also probably mediated via catecholamines in the brain (Dhasmana, Dixit & others, 1972). It is, therefore, possible that the same relations might explain the morphine-induced behavioural excitation of rats.

Sct. Hans Mental Hospital,   I. H. AYHAN*
The Research Laboratory,
Dept. E, DK-400 Roskilde,
Denmark.

July 27, 1973

* Present address: University of Ankara, Faculty of Medicine, Dept. of Pharmacology, Ankara, Turkey.

REFERENCES

AYHAN, I. H. & RANDRUP, A. (1973a). *Psychopharmacologia (Berl.)*, **29**, 317–328.
AYHAN, I. H. & RANDRUP, A. (1973b). *Archs int. Pharmacodyn. Thér.*, **204**, 283–292.
DAVIS, W. M., BABBINI, M. & KHALSA, J. H. (1972). *Res. Comm. Chem. Path. Pharm.*, **4**, 267–279.
DHASMANA, K. M., DIXIT, K. S., JAJU, B. P. & GUPTA, M. L. (1972). *Psychopharmacologia (Berl.)*, **24**, 380–383.
FRIEDMAN, A. H. & WALKER, C. A. (1968). *J. Physiol., Lond.*, **197**, 77–85.
LENOX, R. H. & FRAZIER, T. W. (1972). *Nature, Lond.*, **239**, 397–398.
LUTSCH, E. F. & MORRIS, R. W. (1972). *Experientia*, **28**, 673–674.
MANSHARDT, J. & WURTMAN, R. J. (1968). *Nature, Lond.*, **217**, 574–575.
MORRIS, R. W. & LUTSCH, E. F. (1969). *J. pharm. Sci.*, **58**, 374–376.
PAULY, J. E. & SCHEVING, L. E. (1964). *Int. J. Neuropharmac.*, **3**, 651–658.
REIS, D. J. & WURTMAN, R. J. (1968). *Life Sci.*, **7**, 91–98.
REIS, D. J., RIFKIN, M. & CORVELLI, A. (1969). *Eur. J. Pharmac.*, **8**, 149–152.
ROSSUM, J. M. VAN (1970). *Int. Rev. Neurobiol.*, **12**, 307–383.
SCHEVING, L. E. HARRISON W. H. GORDON, P. & PAULY, J. E. (1968). *Am. J. Physiol.*, **214**, 166–173.
SNEDECOR, G. W. (1956). *Statistical Methods, 5th* Edn. p 97. Iowa: Iowa State Univ. Press.
SVENSSON, T. H. & WALDECK, B. (1970). *Psychopharmacologia (Berl.)*, **18**, 357–365.
SVENSSON, T. H. (1971). *Naunyn-Schmiedebergs Arch. Pharmak.*, **271**, 111–120.
WURTMAN, R. J., AXELROD, J., SEDVALL, G. & MOORE, R. Y. (1967). *J. Pharmac. exp. Ther.*, **157**, 487–492.
ZIGMOND, M. J. & WURTMAN, R. J. (1970). *Ibid.*, **172**, 416–422.