frogs, respectively (Harri, 1972a). This difference is significant at the level of $P < 0.05$. The depletion was retarded after transferring the animals to 25°. This change was significant in winter ($P < 0.001$) but not in summer.

The present results show that the level of brain 5-HT was not related to the sedative action of imipramine. On the other hand, the depletion of 5-HT after *p*CPA, as well as the sensitivity to imipramine-induced sedation were greater in cold-acclimatized frogs and in winter conditions. Because the changes in 5-HT concentrations induced by *p*CPA are dependent on the nerve impulse flow (Andén & Modigh, 1972), the sedative action of imipramine in the frog also seems to depend on brain 5-HT activity. Thus, the sedative action of imipramine in the frog can be modified, not only by drugs which have been found to increase the level of "free 5-HT" (reserpine, MAO inhibitors, fenfluramine) (Lapin & others, 1970; Oxenkrug & Lapin, 1971; Oxenkrug, Osipova & Uskova, 1970), but also by environmental conditions which physiologically alter the release of 5-HT (temperature, season). Conversely, the sensitivity of frogs to imipramine may be used as a measure of the central 5-HT activity.

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A possible interaction of quipazine with central dopamine structures

Quipazine has been described as a representative of a new type of antidepressant agent. In contrast to the tricyclic antidepressants of imipramine type, quipazine does not involve adrenergic mechanisms (Rodriguez & Pardo, 1971), but stimulates the 5-HT receptor both in peripheral tissues (Hong, Sancillo & Vargas, 1969) and in the central nervous system (Rodriguez, 1972; Rodriguez, personal communication).

We have found that quipazine given to rats at a dose of 10·0 mg kg^{-1} (i.p.) induced unusual behaviour patterns, consisting of a few distinct elements. The changes appeared in all experiments, although their intensity varied daily. Shortly after the injection of the drug the locomotor activity of the rats increased, and there was slight tremor, stereotyped head movements, intensive sniffing and rubbing the nose with forepaws.

7 to 15 min after the injection the locomotor activity subsided; the subjects stirred their forepaws and turned round still sitting on their hindpaws. At this time there appeared episodes of rapid movements of forepaws and stereotyped head movements,

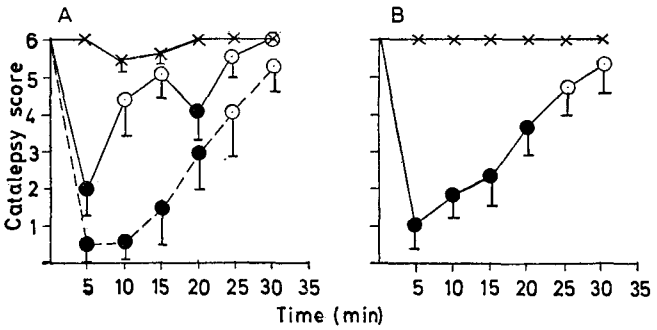

FIG. 1. The influence of quipazine at the doses of 10·0 (○———○) or 20·0 (○- - - -○) mg kg^{-1} on the neuroleptic (x———x) induced catalepsy evaluated by the method of Delini-Stula & Morpurgo (1968); catalepsy score was multiplied by two in comparison with original method. Spiroperidol (A) and reserpine (B) were injected at the doses of 0·5 and 5·0 mg kg^{-1} respectively. Black circles indicate the results statistically significant (Student's *t*-test). Each group consisted of 6 rats.

giving the impression of "piano playing." The rats sniffed and occasionally gnawed intensively. During the next 10 min the rats remained almost completely immobile, the episodes of sniffing and gnawing became less frequent and less intensive, but the episodes of "piano playing movements" remained frequent. 25 to 35 min after the injection the rat behaviour was almost normal (walking, rearing, grooming) but the "piano playing movements" sometimes appeared.

The anti-5-HT drugs, cyproheptadine and methysergide (5·0 mg kg,$^{-1}$ by mouth and i.p. respectively) inhibited all the symptoms observed after quipazine administration. A butyrophenone derivative, spiroperidol (0·5 mg kg^{-1} i.p.) also prevented the quipazine syndrome completely, whereas other butyrophenones, haloperidol (1·0 mg kg^{-1} i.p.) and pimozide (1·2 mg kg^{-1} i.p.) abolished the hypermotility and significantly depressed the intensity of gnawing and sniffing. Haloperidol also prevented the "piano playing movements".

The stereotyped behaviour promoted by quipazine was unaffected by phenoxybenzamine (10·0 mg kg^{-1} i.p.), and reserpine (5·0 mg kg^{-1} s.c.) only slightly depressed the hyperactivity. A tryptophan hydroxylase inhibitor, *p*-chlorophenylalanine (316 mg kg^{-1}, i.p.) given three days before quipazine potentiated the hypermotility and intensity of "piano playing movements" induced by the latter agent, but did not affect the intensity and duration of sniffing and gnawing.

A subthreshold dose of apomorphine (0·1 mg kg^{-1} s.c.) potentiated the effects produced by 10·0 mg kg^{-1} of quipazine; it also promoted the appearance of stereotyped behaviour after a low dose of quipazine (2·5 mg kg^{-1}), which given alone produced no behavioural changes.

Some effects observed after quipazine administration are similar to those described after intraperitoneal injection of 5-hydroxytryptophan, or after administration of 5-HT into brain structures (Ernst, 1969; Hadzovic & Ernst, 1969). Our observations seem to confirm the view that quipazine stimulates 5-HT receptors. As *p*-chlorophenylalanine does not inhibit the effects of quipazine, it seems that the latter compound stimulates the 5-HT receptors directly.

Some features of quipazine-induced stereotypy, as hypermotility, sniffing and gnawing, are regarded as a result of stimulation of dopamine receptor (Ernst, 1969). We therefore investigated the influence of quipazine on spiroperidol-induced catalepsy. Quipazine inhibited the catalepsy caused by the dopamine receptor blockade in a dose-dependent manner (Fig. 1); the anticataleptic effect was short-lasting and

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.

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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