BAUMGARTEN, H. G., EVETTS, K. D., HOLMAN, R. B., IVERSEN, L. L., VOGT, M. & WILSON, G. (1972). *J. Neurochem.*, **19**, 1587–1597.

BAUMGARTEN, H. G. & LACHENMAYER, L. (1972). *Z. Zellforsch.*, **135**, 399–414.

DIAZ, J.-L. & HUTTUNEN, M. O. (1972). *Psychopharmacologia* (Berlin), **23**, 363–372.

MAICKEL, R. P. & MILLER, F. P. (1966). *Analyt. Chem.*, **38**, 1937–1938.

The dependence of imipramine-induced sedation upon central 5-hydroxytryptomine-like activity in the frog

Both 5-hydroxytryptamine-like and adrenaline-like actions of antidepressants are probably necessary for their therapeutic effect (Lapin & Oxenkrug, 1969). However, in the frog, the sedation and the typical twitches of the limbs caused by antidepressants like imipramine, most probably reflect the activation of the central 5-HT processes (Lapin & Oxenkrug, 1969). This hypothesis is based, not only on the minor role of noradrenaline in the frog brain, but also on the observations that the potentiation of the sedative effects of imipramine by reserpine or monoamine oxidase (MAO) inhibitors, or both, is related to an increase in "free brain 5-HT", which potentiation is blocked by 5-HT antagonists, while drugs influencing mainly the adrenergic processes are without any apparent behavioural effect in amphibians (e.g., chlorpromazine, amphetamine, AW-151129*) (Brodie, Bogdanski & Bonomi, 1964; Lapin, Oxenkrug & others, 1970; Oxenkrug & Lapin, 1971). Moreover, the rapid utilization of brain 5-HT *in vivo* (Harri, 1972a, b) and *in vitro* (Brodie & others, 1964) compared with that of adrenaline, supports the predominance of 5-HT processes in the brain of amphibians.

In the frog, the central 5-HT-like activity is greatly influenced by season and temperature acclimation (Harri, 1972a). Thus, it was of interest to study whether these changes are related to the sedative action of imipramine.

Frogs (*Rana temporaria*) were acclimatized to 5° (cold-acclimatized) and to 25° (warm-acclimatized) for at least 20 days before the experiments, in winter (February) and in summer (May). Imipramine, as aqueous solution, was injected into the dorsal lymph sac, and the onset of sedation (loss of the righting reflex) and its duration was recorded.

The durations of the sedation caused by a certain dose of imipramine were significantly longer in winter than in summer frogs ($P < 0{\cdot}001$; Mann-Whitney U-test) and also significantly longer in cold-acclimatized than warm-acclimatized animals in winter ($P < 0{\cdot}01$) but not in summer. The equipotent doses corresponding to the sedation for 4 h were 35 and 40 mg kg^{-1} for the winter frogs acclimatized to 5° and to 25°, and 54 and 57 mg kg^{-1} for the summer frogs, respectively. With these doses imipramine did not depress the limb movements or the pain and touch responses markedly. It only prevented the frogs from turning around on their limbs. This indicates that in spite of the high doses used the local anaesthetic action of imipramine is unimportant in influencing the results. On the other hand, chlorpromazine caused a loss of the righting reflex only with doses (over 150 mg kg^{-1}) which depressed all body movements and also were lethal.

The level of 5-HT was 1·93–3·06 $\mu g\ g^{-1}$ in the brain of winter frogs and 3·24–4·58 $\mu g\ g^{-1}$ in the summer frogs (Harri, 1972a). In the winter frogs, the level temporarily increased in warmth but was returned to the original level after 20 days, when the animals were used in experiments with imipramine.

When the 5-HT biosynthesis was inhibited with *p*-chlorophenylalanine (*p*CPA) (200 mg kg^{-1}) 2 h before killing the animals, its level in the brain was depleted by $1{\cdot}27 \pm 0{\cdot}042$ and $0{\cdot}89 \pm 0{\cdot}162\ \mu g\ g^{-1}$ in the cold acclimatized winter and summer

* 5-(*p*- Chlorphenyl)- 2,3,5,6, - tetrahydroimidazo (1, 2-c) quinazoline.

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.

The work has been supported by the Emil Aaltonen Foundation.

Zoophysiological Laboratory,
Department of Zoology,
University of Turku,
SF-20500 Turku 50, Finland

MIKKO N. E. HARRI

May 24, 1973

REFERENCES

ANDÉN, N.-E. & MODIGH, K. (1972). *J. Neur. Transm.*, **33**, 211–222.

BRODIE, B. B., BOGDANSKI, D. F. & BONOMI, L. (1964). In *Comparative Neurochemistry*. pp. 367–377. Editor: Richter, D., Oxford-London-New York-Paris.

HARRI, M. N. E. (1972a). *Comp. gen. Pharmac.*, **3**, 11–18.

HARRI, M. N. E. (1972b). *Ibid.*, **3**, 101–112.

LAPIN, I. P. & OXENKRUG, G. F. (1969). *Lancet*, **1**, 132–136.

LAPIN, I. P., OXENKRUG, G. F., OSIPOVA, S. V. & USKOVA, N. V. (1970). *J. Pharm. Pharmac.*, **22**, 781–782.

OXENKRUG, G. F. & LAPIN, I. P. (1971). *Ibid.*, **23**, 971–972.

OXENKRUG, G. F., OSIPOVA, S. V. & USKOVA, N. V. (1970). In *Serotoninergic Processes in Action of Psychotropic Drugs.*, pp. 45–57. Editor: Lapin, I. P. Leningrad.

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,