activity and such a relationship was not observed between numbers of substitution of N and the antipyretic activity.

All compounds showed an inhibitory effect on rat paw edema induced by carrageenin. The activity was more potent in the compounds that have methyl in N of side chain than in those of ethyl or ethanol. In this anti-edematous effect, it appears that numbers of substitution of N have little relationship with the activity, but the length of alkyl of substitution contributed a great deal to the activity. Though the central nervous system may not play a great role in peripheral paw edema, the order of anti-edematous activity was different from that of analgesic activity. On the erythema induced by ultraviolet irradiation, the compounds did not exhibit an inhibitory action, similar to such basic compounds as mepirizole. It was demonstrated by Adams et al (1, 2), Winder et al (3) and Winter (4) that there was a reasonable correlation between anti-erythemic and anti-rheumatic activities. These compounds may have no effect on subacute and chronic inflammation.

From the above results, it is conceivable that 1-(m-chlorophenyl)-3-carbamoyl-5-methoxypyrazole derivatives do possess the pharmacological features of analgesic and basic anti-inflammatory agent. Out of the seven derivatives, PZ-177 was the most potent in analgesic and anti-inflammatory activities and the toxicity was less than that of aminopyrine. A detailed pharmacological study of PZ-177 will be reported elsewhere.

REFERENCES

- 1) ADAMS, S.S.: *J. Pharm. Pharmacol.*, **12**, 251 (1960); 2) ADAMS, S.S., CLIFFE, E.E., LESSEL, B. AND NICHOLSON, J.S.: *Nature*, **200**, 271 (1963); 3) WINDER, C.V., WAX, J., BURN, V., BEEN, M. AND ROSIERE, C.E.: *Archs int. Pharmacodyn. Thér.*, **116**, 261 (1958); 4) WINTER, C.A.: *Progress in Drug Research*, Edited by JUCKER, E., vol. 10, p. 139, Birkhauser, Basel (1966)

CORRELATION BETWEEN THE 5-HYDROXYTRYPTAMINE CONTENTS IN THE BRAIN AND DEGREES OF SENSORY, AND LOCOMOTOR ACTIVITIES IN THE RAT

Tsutomu KAMEYAMA, Tsuyoshi SHIGEHISA*
and Toshitaka NABESHIMA

*Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences,
Meijo University, Tempaku-ku, Nagoya 468, Japan*

Accepted September 4, 1975

Using an operant conditioning technique and open-field test, Kameyama and Shigehisa (1, 2) have shown that animals' sensory, and spontaneous locomotor activities may be altered by means of imipramine, in relation to initial levels of these activities. Biochemical

* Present address: The Psychoacoustics Section, NASA Langley Research Center, Hampton, Virginia, 23665, U.S.A.

studies (3-5) suggest that imipramine is more efficient than norepinephrine in blocking the reuptake of 5-hydroxytryptamine (5-HT) by nerve endings. Sheard *et al.* (6) indicated that tertiary amines, imipramine, amitriptyline and chlorimipramine have a significant depressant effect on the firing rate of 5-HT containing neurons in the brain. Thus, a possible mechanism of the effect of imipramine on behavior may involve a change in the content of this amine in the brain. Behavioral depression could be approached by examining the change in animals' receptivity, as well as reactivity, to sensory stimuli (1, 2). In this study, a psychophysical approach to depression, previously made (1, 2), was extended in an attempt to investigate a possible mechanism of alteration, caused by imipramine, in sensory and motor activities, which depends on the initial level of activities. In short, the way in which brain 5-HT may have a specific measurable correlation to these behavioral parameters was investigated.

Male rats of Sprague-Dawley strain, having initial body weights of 150-200 g, were used for an open-field test and for an auditory threshold determination by a method of limits using an operant conditioning technique (1, 2). A water-deprived rat was trained to bar press under a variable-ratio (VR)-10 reinforcement schedule. Each reinforcement, a 3-sec dipper presentation, was accompanied by a 1.5 sec pure tone (3 KHz, 100 dB SPL). The onsets of the tone and the dipper presentation were simultaneous. Only within this 3-sec of dipper presentation could the rat get water reinforcement (0.01 ml), by sticking its nose into the dipper area. The ascending method was used with the test tone intensity ranging from 0-100 dB, with 2-5 dB steps randomly spaced. The test tones (intensity variable) and the training tones (intensity constant at 100 dB) were alternately presented, with reinforcement under VR-10 schedule. The intensity of the test tones was increased in each trial until the animal made responses (dipper approaches only within 3-sec after the tone onset) for more than 3 consecutive trials. The mean of the lowest tone intensity at which the animal responded and the highest tone intensity at which the animal failed to respond, was taken as threshold. Prior to the threshold determination, each animal was placed in an open-field and ambulation, rearing, defecation and grooming scores were obtained during a 3-min period. After the behavioral measurements each animal was sacrificed immediately by decapitation, the brain was removed, and the contents of 5-HT in two portions, the telencephalon and the other brain areas (pooled) were determined fluorometrically according to the method of Snyder *et al.* (7).

For each animal there were auditory threshold, locomotor activity and 5-HT content measures. Correlation coefficients were calculated between the content of 5-HT ($\mu\text{g/g}$ wet weight) and auditory threshold (in dB), bar-press speed (number of bar-presses/min), ambulation, rearing, defecation and grooming scores. As shown in Table 1, Pearson product-moment coefficients of correlation show that there was a significant "positive" correlation between telencephalic 5-HT and auditory threshold ($p < 0.05$), and non-telencephalic 5-HT and ambulation ($p < 0.05$). In addition, there was a significant "negative" correlation between telencephalic/non-telencephalic ratio of 5-HT and defecation ($p < 0.05$). On the contrary, there was no such correlation between whole brain 5-HT and each

TABLE 1. Correlation between 5-hydroxytryptamine (5-HT) contents in the brain and behavioral measures (Pearson product-moment coefficients of correlation)

5-HT contents		Auditory thresholds	Bar-press speed	Ambulation	Rearing	Defecation	Grooming
Telencephalon	r	0.616 (2.347*)	-0.379 (1.228)	0.398 (1.303)	-0.118 (0.355)	-0.204 (0.624)	0.205 (0.627)
Remaining brain areas	r	0.182 (0.555)	-0.266 (0.828)	0.628 (2.420*)	-0.275 (0.858)	0.455 (1.534)	-0.069 (0.208)
5-HT ratio ^a	r	0.243 (0.751)	0.011 (0.032)	-0.472 (1.608)	0.269 (0.836)	-0.669 (2.686*)	0.293 (0.918)
Whole brain	r	0.497 (1.718)	0.262 (0.814)	0.518 (1.819)	-0.197 (0.602)	0.105 (0.315)	0.124 (0.375)

^a 5-HT ratio=(5-HT content in telencephalon/5-HT content in remaining brain areas).

()=t; *p<0.05, df=9, Two-tailed tests.

behavioral parameter.

These results indicate that the greater the content of 5-HT in the telencephalon the less the sensory activity and the less frequent the defecation, and that the greater the 5-HT content in non-telencephalic areas the greater the ambulation and more frequent the defecation. There is the possibility that the 5-HT content in the auditory area in the telencephalon may be related to sensory activity.

In order to demonstrate further that the content of 5-HT in the telencephalon is negatively correlated with auditory sensitivity, the rats pretreated with DL-p-chlorophenylalanine (pCPA) were subjected to threshold determination. Table 2 shows that a pCPA treatment (3×100 mg/kg, i.p.) caused a significant decrease in 5-HT content in the telencephalon ($t=17.31$, $df=19$, $p<0.001$, two-tailed test) and in auditory threshold ($t=5.59$, $df=9$, $p<0.001$, two-tailed test), as compared with pretreatment measures. This finding gives support to the hypothesis that the greater the content of 5-HT in the telencephalon the less the sensory activity, as far as the auditory modality is concerned. In addition, our previous results indicated that animals' sensory activities and spontaneous locomotor activities can be altered by means of imipramine, in relation to initial level of these activities (1, 2). Thus, the present results are consistent with the suggestion that a possible mechanism

TABLE 2. Effect of p-chlorophenylalanine (pCPA) on auditory thresholds and telencephalic contents of 5-HT

pCPA treatment	Auditory thresholds (in dB)	5-HT contents (μ g/g wet weight of tissue)
Before	72 $\pm$ 14	(0.52 $\pm$ 0.05) ^a
After	37 $\pm$ 11	0.20 $\pm$ 0.03

Each value represents mean $\pm$ S.D. of 10 rats. Each animal was treated i.p. with 100 mg/kg/day of pCPA for 3 consecutive days. For each animal there were two threshold measures, one 12 hr before, and the other 72 hr after the first administration of pCPA. The 5-HT contents were determined 6 hr after threshold determination. ^aThis datum was obtained from 11 saline-treated rats with a mean auditory threshold of 77 $\pm$ 3.

of the effects of imipramine on behavior may involve a change in the level of 5-HT at receptor site in the brain. A further investigation is now underway to determine the effects of 5-hydroxytryptophan, a 5-HT precursor, and related catecholamines on these behavioral measures.

REFERENCES

- 1) KAMEYAMA, T., SHIGEHISA, T.: *Japan. J. Pharmacol.*, **23**, Suppl. 62 (1973); 2) KAMEYAMA, T., SHIGEHISA, T.: *Japan. J. Pharmacol.*, **23**, Suppl. 63 (1973); 3) CARLSSON, A., CORRODI, H., FUXE, K., HÖKFELT, T.: *Europ. J. Pharmacol.*, **5**, 357 (1969); 4) CARLSSON, A.: *J. Pharm. Pharmacol.*, **22**, 729 (1970); 5) SHASKAN, E.G., SNYDER, S.H.: *J. Pharmacol. exp. Ther.*, **175**, 404 (1970); 6) SHEARD, M.H., ZOLOVICK, A., AGHAJANIAN, G.K.: *Brain Res.*, **43**, 690 (1972); 7) SNYDER, S.H., AXELROD, J., ZWEIG, M.: *Biochem. Pharmacol.*, **14**, 831 (1965)

PRE- AND POST-SYNAPTIC ORIGIN OF LITHIUM-INDUCED ACUTE BLOCKADE ON ADRENERGIC TRANSMISSION IN RABBIT HEART

Yoshimi MISU, Yasushi KURAISHI and Hiroshi TAKAGI

*Department of Pharmacology, Faculty of Pharmaceutical Sciences,
Kyoto University, Sakyo-ku, Kyoto 606, Japan*

Accepted September 18, 1975

Lithium is being clinically prescribed for patients in the manic phase of manic depressive psychosis. There are reports that lithium interferes with metabolism (1-3) and release of noradrenaline (4) in the brain and that iontophoretically applied lithium antagonises a noradrenaline-induced inhibition of hippocampal spontaneous firing activity in rats (5). The present experiment was carried out to investigate the action of lithium on the adrenergic transmission in perfused rabbit hearts with sympathetic trunks as a model. Pre- and post-synaptic responses to nerve stimulation could thus be obtained simultaneously.

The hearts with bilateral sympathetic trunks from 33 rabbits of either sex, 1.6 to 2.0 kg, were isolated and perfused with Krebs bicarbonate solution gassed with 5% CO₂ in oxygen as described previously (6). Temperature of the solution was kept at 30°C. The perfusion pressure was 60 cm H₂O and the rate was 10 to 15 ml/min. The extreme upper thoracic region of nerves was stimulated through ring electrodes similar to those described by Garry and Gillespie (7) with supramaximal rectangular pulses of 3.5 msec duration at a frequency of 30 Hz. The nerves were stimulated 6 times, each of 30 sec duration with a 30 sec resting period. This 6 min stimulation-rest procedure is referred to as the 1st procedure. The 2nd procedure was performed similarly 30 min after the beginning of the 1st procedure. The venous effluent was collected for each 6 min procedure period and noradrenaline was measured fluorometrically by the methods of Anton and Sayre (8).

Some hearts were suspended by means of a perfusion apparatus KN-206 (Natsume)