Pharmacology Biochemistry & Behavior, Vol. 5, pp. 383–385.

The Tryptolines: Effect of Intraventricular Administration on Spontaneous Motor Activity of Rats

R. A. GREEN,[1] J. D. BARCHAS,[2,3] G. R. ELLIOTT,[2,4] J. S. CARMAN AND R. J. WYATT

Laboratory of Clinical Psychopharmacology, Division of Special Mental Health Research, IRP, NIMH Saint Elizabeths Hospital, Washington D.C. 20032

and

[2]*Laboratory of Behavioral Neurochemistry, Department of Phychiatry and Behavioral Science Stanford School of Medicine, Stanford, CA 94305*

(Received 24 June 1976)

GREEN, R. A., J. D. BARCHAS, G. R. ELLIOTT, J. S. CARMAN AND R. J. WYATT. *The tryptolines: effect of intraventricular administration on spontaneous motor activity of rats.* PHARMAC. BIOCHEM. BEHAV. 5(4) 383–385, 1976. – The pharmacologic properties of the tryptolines, hindered analogues of the tryptamines, were studied behaviorally in rats. Following intraventricular injections, it was found that spontaneous motor activity decreased markedly during the initial 25 mins when compared with saline. Since both the tryptolines and tryptamines have been shown to be inhibitors of 5-hydroxytryptamine uptake, it may be possible that these compounds are acting indirectly through an effect on the serotonergic system.

Tryptolines Tryptamine 5-HT Serotonin Motor activity

RESEARCH into hypothesized biological mechanisms underlying schizophrenia has, in the last few years, focused considerable attention on tryptamine and its derivatives. In particular, a number of studies have centered upon O- and N-methylated products, such as the hallucinogen dimethyltryptamine (DMT) [11, 15, 16]. Recently, attention has been brought to another class of compounds – the tryptolines, or tetrahydro-β-carbolines [1, 2, 8, 14]. One interesting aspect of these compounds, as illustrated in Fig 1, is that they constitute sterically hindered analogues of the tryptamines. The importance of this similarity is clearly illustrated in the finding that tryptolines are potent inhibitors or 5-hydroxytryptamine uptake in rat-brain homogenates [3, 6, 7, 12]. We, therefore, decided to compare the effects of several tryptamines with those of their tryptoline analogues. For this purpose, we monitored changes in spontaneous motor activity of rats receiving intraventricular injections of the compounds, since this may offer a behavioral index of the central pharmacologic properties of these drugs.

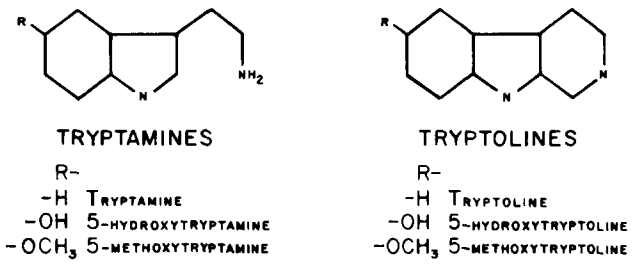

FIG. 1. Structural similarities.

METHOD

Animals and Procedure

Twenty-five male, Sprague-Dawley rats (Zivic-Miller), weighing approximately 210 g, were studied in a repeated-measures design. A polyethylene cannula was surgically

[1] Send reprint requests to: R. A. Green, William A. White Building, Room 536, Saint Elizabeths Hospital, Washington, D.C. 20032.
[2] Laboratory of Behavioral Neurochemistry, Department of Psychiatry and Behavioral Science, Stanford School of Medicine, Stanford, CA 94305.
[3] J. D. Barchas holds Research Scientist Development Award, MH 24171.
[4] G. R. Elliott is supported by Biosciences Training Grant, MH 8304.

implanted into the right ventricle of each rat (2.0 mm lateral, 2.0 mm posterior to the bregma, and 3.5–4.0 mm below the surface of the skull), and one week was allowed for recovery. The position of the cannula was verified histologically at the end of the experiment by injection of 5 μl of dye just prior to sacrificing the animal. Each rat was housed separately throughout the experiment with food and water ad lib. A constant temperature and a 12:12 light:dark cycle (lights on at 6:00 a.m.) were maintained.

Each rat served as its own control, receiving a different drug on each of seven trials. The time of testing was held constant for each rat on successive trials (either at 9 or 10:30 a.m.) and the order of injections was systematically counterbalanced. A 3 or 4 day intertrial interval was allowed for tissue clearance of the previous drug. The drugs to be injected were dissolved in sterile saline and adjusted to a pH of 6.5 to avoid precipitation. All doses were 50 μg, delivered in a volume of 5 μl via a 50 μl Hamilton microsyringe. The drugs included saline (control), tryptamine, tryptoline, 5-hydroxytryptamine, 5-hydroxy-tryptoline, 5-methoxytryptamine, and 5-methoxytryptoline.

Horizontal locomotor activity of each rat was monitored in an eight-celled motility meter, utilizing infra-red sensors (Motron Co., Sweden) [10]. Immediately following the intraventricular injection, the rat was placed into the motility meter. Light beam crossings were counted and automatically recorded on printing counters at 5 min intervals for 1 hr. At the end of the hour, the animal was returned to his cage and the data tabulated.

RESULTS

Analyses of variance (ANOVA) were performed for each 5 min interval. Following the finding of a significant overall F ratio in the ANOVA, a Dunnetts *t*-test was used to test the significance level of any particular treatment compared to saline controls [13].

Regardless of the treatment condition, overall motility of the rats declined rapidly during the first 30 min. Although the variability was high, all of the drug treatments enhanced this decline during the first 15 min compared to saline. When the data from a preliminary study (N = 22) of 5-hydroxytryptoline and 5-methoxytryptoline are combined with these data, the decrements in activity are significant through 25 min (Table 1). Comparisons between the tryptamines and their tryptoline analogues showed no statistical differences. Beyond 25 min, no significant differences were observed.

DISCUSSION

Although there were no significant differences between the effects of the various drugs, it should be noted that 5-hydroxytryptamine and 5-methoxytryptamine produced the largest decrements in activity, followed by a slow increasing trend toward the control levels. In contrast, the remainder of the drugs produced a monotonically decreasing curve of activity, similar to, although steeper than, the saline activity curve. It could be argued from these data that the observed decrement in activity might be a non-specific effect, unrelated to the drug. However, the lack of difference between sodium creatinine sulfate, a control for 5-hydroxytryptamine-creatinine sulfate injections, and saline in a preliminary study, tends to discount this possibility. Further study of this alternative is needed.

Since both the tryptolines [7] and tryptamines [6] have been shown to be inhibitors of 5-hydroxytryptamine uptake, it is possible that these compounds are acting indirectly through an effect on the serotonergic system. Following IP injections of 5-methoxytryptoline brain serotonin concentrations were significantly increased in one study [4,9]. However, another study in the same laboratory showed no change following intraventricular administration [5]. The specific mode of action will require further study. It will be of particular interest to see how the tryptolines affect the systems which are involved in the regulation of serotonergic activity, including mechanisms of synthesis, uptake, storage, release and metabolism.

TABLE 1

MEAN ACTIVITY ± SE PER 5-MIN PERIOD

	Group 1 N = 25							Combined N = 47		
	Saline	Tryptamine	Tryptoline	5-Hydroxy-tryptamine	5-Hydroxy-tryptoline	5-Methoxy-tryptamine	5-Methoxy-tryptoline	Saline	5-Hydroxy-tryptoline	5-Methoxy-tryptoline
5 Min		†	†	†	†	†	†		†	†
Mean	73.92	53.44	48.20	52.52	54.88	49.60	57.96	71.79	56.19	58.11
SE	4.31	5.77	4.00	4.82	6.11	4.06	5.67	3.23	4.25	4.13
10 Min			*	†	*	†	*		†	†
Mean	37.24	26.96	22.04	14.72	22.08	12.40	24.28	44.55	26.34	28.85
SE	5.27	4.96	4.39	2.79	4.08	2.98	4.95	4.26	3.73	4.47
15 Min				*		†			†	†
Mean	28.16	22.40	22.64	14.84	18.72	13.36	19.40	35.15	17.77	24.28
SE	3.75	3.33	3.55	3.54	3.01	3.26	3.19	3.23	2.02	3.36
20 Min									†	*
Mean	26.36	21.00	16.72	16.16	20.52	17.04	16.76	27.89	17.21	20.85
SE	3.46	3.50	3.17	3.53	2.95	3.98	2.86	2.72	1.83	2.95
25 Min									*	
Mean	18.80	21.92	20.92	19.96	18.84	11.88	19.64	26.36	17.49	21.34
SE	2.53	3.12	2.68	3.40	2.89	2.72	3.70	2.89	2.02	2.66

*$p<0.05$.
†$p<0.01$ Compared to Saline Controls.

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