Prolongation of Hypnosis by 5-Hydroxytryptamine (Serotonin)

SHORE, SILVER and BRODIE[1], in a recent note in this journal, have described experiments in which the sleeping times of mice pretreated with 5-hydroxytryptamine (5-HT) were compared with those given hexobarbitone alone. The mean sleeping time for the mice given 5-HT before the hexobarbitone was found to be some 300% longer than that of the controls. Moreover, the hypnosis-prolonging effect of 5-HT was substantially diminished when mice were given prior to 5-HT the compound, lysergic acid diethylamide, which is known to antagonize several actions of 5-HT and which has also the interesting property of producing in man mental disturbances resembling schizophrenia. These observations were held to support the concept advanced by WOOLLEY and SHAW[2] "that serotonin has an important role to play in mental processes and that the suppression of its action results in a mental disorder".

Now when they put forward this idea, WOOLLEY and SHAW added: "Of course, this may be the wrong inference from the pharmacological findings... The mental disturbances may be no more than the reflection of diminished blood flow which they (certain chemical analogues of 5-HT) may cause in the brain. To this objection there is as yet no adequate answer, and it may be the true explanation." The possibility that the hypnosis-prolonging action of 5-HT is secondary to an action on blood vessels must, I believe, still be considered in view of some of the following observations.

Like SHORE, SILVER, and BRODIE, I have found that 5-HT can potentiate considerably the hypnotic effect of a barbiturate. I would agree with them that this effect is unlikely to be due to a specific interference with the detoxication of barbiturates, for I have found that the hypnotic effect of chloral hydrate is similarly increased in duration by 5-HT (Table). This property of 5-HT does not appear to be highly specific, however. I have noted it, not only with bufotenine and tryptamine itself, but also with several other compounds which do not resemble 5-HT nearly so closely, e.g. adrenaline and histamine (Table).

Effect of various compounds on the duration of the sleep produced in mice by the intraperitoneal injection of either cyclobarbitone (100 mg/kg) or chloral hydrate (250 mg/kg).
Each compound was injected either intraperitoneally (i.p.) or subcutaneously (s.c.) 10 min before the hypnotic. The sleeping times given are the means for groups of 10 mice – in each experiment the hypnotic was given to 20 mice, 10 of which had already received the compound under investigation. The figure in brackets after each mean sleeping time is the standard error for the 10 observations. The 't' test shows most of the differences to be significant at the P = 0·01 level and almost all at the P = 0·1 level.

(1) Experiments with cyclobarbitone

Pre-treatment			Sleeping time: Treated group	Sleeping time: Control group
			min	min
5-HT	20 mg/kg	i.p.	80 (7·8)	33 (2·2)
5-HT	20 mg/kg	s.c.	88 (8·8)	47 (7·3)
5-HT	20 mg/kg	s.c.	67 (19·8)	25 (4·4)
5-HT	20 mg/kg	s.c.	61 (10·1)	36 (3·7)
Histamine	20 mg/kg	i.p.	68 (6·7)	42 (5·0)
Histamine	20 mg/kg	i.p.	73 (3·9)	44 (4·9)

(2) Experiments with chloral hydrate

Pre-treatment			Sleeping time: Treated group	Sleeping time: Control group
			min	min
5-HT	20 mg/kg	i.p.	86 (12·1)	20 (2·3)
Bufotenine	20 mg/kg	i.p.	81 (10·4)	22 (2·8)
Tryptamine	20 mg/kg	i.p.	37 (3·1)	22 (2·4)
Histamine	10 mg/kg	i.p.	38 (3·1)	26 (3·1)
Histamine	10 mg/kg	i.p.	51 (3·9)	26 (4·2)
Histamine	10 mg/kg	s.c.	54 (5·1)	32 (3·7)
Adrenaline	5 mg/kg	i.p.	98 (13·0)	35 (5·6)
Adrenaline	5 mg/kg	s.c.	70 (19·2)	20 (3·3)
Adrenaline	3 mg/kg	i.p.	65 (9·6)	24 (2·3)
Adrenaline	3 mg/kg	s.c.	39 (4·1)	31 (4·9)

Other workers have published similar findings. For example, WERLE and LENTZEN[3] showed that various vasoactive drugs (histamine, vasopressin, adrenaline and sympatol, but not acetylcholine or adenylic acid) could deepen and prolong the sleep produced in the rabbit by evipan and other, unrelated hypnotics. Certain carbohydrate metabolites[4], colchicine[5], and even some purely inorganic agents[6] – notably potassium salts[7] – have been found capable of prolonging the hypnotic effect of barbiturates.

If, as seems likely[4], the prolongation of barbiturate anaesthesia by such agents as lactate and glutamate is brought about through the mediation of adrenaline, it follows that almost all of the known hypnosis-prolonging agents are drugs which exert, directly or indirectly, powerful effects on the circulatory system. It therefore seems possible that the ability of 5-HT to prolong hypnosis may be due to a relatively unspecific, vascular effect.

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Zusammenfassung

Die Angabe, dass 5-Oxytryptamin (Serotonin) die Chloralhydrat- oder Barbitursäure-Hypnose bei Mäusen verlängern kann, wurde bestätigt. Da aber Stoffe wie Adrenalin und Histamin den gleichen Effekt zeigten, erscheint es möglich, dass die hypnoseverlängernde Eigenschaft des 5-Oxytryptamin auf einen relativ unspezifischen, vaskulären Effekt zurückzuführen ist.

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[3] E. WERLE and J. LENTZEN, Arch. exper. Path. Pharmakol. *190*, 328 (1938).

[4] P. D. LAMSON, M. E. GREIG, and L. WILLIAMS, J. Pharmacol. exper. Therap. *106*, 219 (1952).

[5] R. W. BALEK, J. J. KOCSIS, and E. M. K. GEILING, J. Pharmacol. exper. Therap. *116*, 5 (1956).

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