The Influence of Inhibitors of Amine Metabolism on the Effects of Serotonin and its Metabolites on Photic Evoked Potential in Rabbits

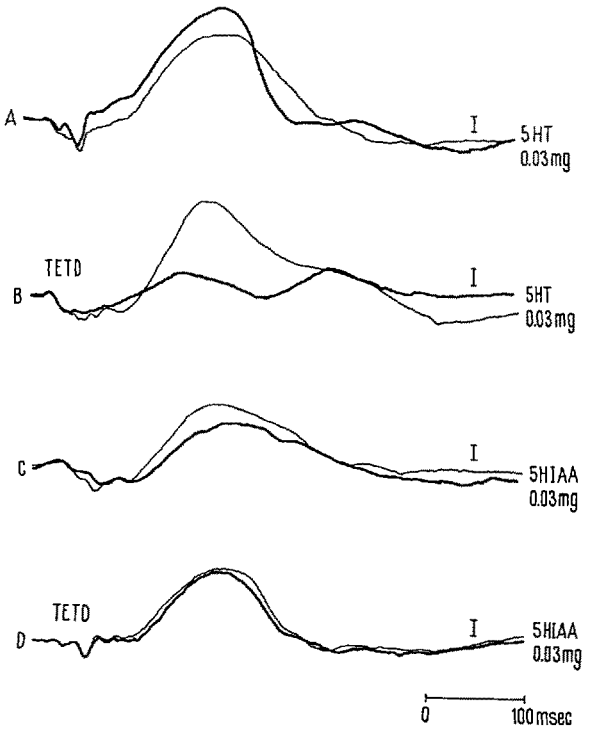
The visual pathway[1] and the sleep-activating mechanism[2] are presumably modulated by endogenous serotonin (5HT). 5HT is metabolized by monoamine oxidases (MAO) with the formation of 5-hydroxyindoleacetaldehyde (5-hydroxytryptaldehyde, 5HTA), which is primarily converted into 5-hydroxyindoleacetic acid (5HIAA) by aldehyde dehydrogenase and, to a lesser extent, into 5-hydroxytryptophol (5HTOL) and other metabolites[3]. Recent experiments[4–7] suggest that the transformation of 5HT to a deaminated product may contribute to its CNS effects. In these experiments, the dose-response curve for intraventricular injection of 5HT, 5HTOL and 5HIAA on the photic evoked potential in rabbits showed that 5HTOL and 5HIAA were as potent as 5HT. In addition, pretreatment with 2 different inhibitors of amine metabolism, N-benzyl-N-methylprop-2-ynylamine (pargyline) and tetraethylthiuram disulfide (TETD), markedly altered the effects of 5HT without influencing the effects of its metabolites.

Materials and methods. Non-anesthetized rabbits (New Zealand, male 1–2 kg) were chronically implanted with cortical electrodes and a lateral ventricle injection cannula ipsilateral to the site of recording. 50 optic cortex potentials (monopolar recording) evoked by 10 μsec red flashes (0.5 stim/sec) were added, by a Computer of Average Transients every 2–5 min. 5-hydroxyindoles were injected intraventricularly (5-hydroxyindoles do not readily cross the blood-brain barrier) dissolved in 0.2 ml of artificial cerebrospinal fluid (see [7]). The evoked potential consists of an initial complex of fast positive potentials, a slow negative wave (SNW) and a slow positive wave.

Results. Fast potentials were depressed by the three 5-hydroxyindoles tested (5HT, 5HTOL and 5HIAA) at all dose levels; this depression was more pronounced with 5HTOL than with 5HIAA or 5HT. This depression occurred shortly after the injection of 5HTOL or 5HIAA; a transient enhancement of fast potentials was noted 2–5 min after injection of 5HT (Figure A) or 5HTA[5]. 5HT reduced the SNW amplitude at all doses tested (Table). The onset of the SNW depression occurred 15–20 min after injection of 0.03 mg of 5HT, and it was preceded by a transient enhancement of the SNW (13% increase at 2 min) (Figure A). The SNW depression began shortly after injection at the higher doses. 5HTOL depressed the SNW at all doses tested (0.03, 0.14 and 0.28 mg) more than comparable doses of 5HT or 5HIAA. 5HIAA (0.03 and 0.14 mg) also depressed the SNW. In contrast, higher doses of 5HIAA (0.28 mg) transiently enhanced the SNW (Table, 21–30 min) without depression at the intervals tested. In conclusion, low doses of 5HTOL and 5HIAA were as effective as 5HT in reducing the SNW amplitude, whereas, only 5HTA[5] mimicked the initial SNW enhancement induced by 5HT. The pharmacological activity of 5HTOL and 5HIAA, together with the delay in the onset of the SNW depression induced by low doses of 5HT, suggests a possible participation of 5HT metabolites in its central action.

To test this hypothesis, the effects of the 5-hydroxyindoles (at the dose of 0.03 mg) were studied in animals pretreated with the MAO inhibitor pargyline (100 mg/kg/24 h before) or the aldehyde dehydrogenase inhibitor TETD (250 mg/kg/24 h before). Pargyline pretreatment reduced the initial enhancement and prevented the late depression of the SNW induced by 5HT, it did not modify the SNW depression induced by 5HIAA and hastened the SNW depression induced by 5HTOL. These results suggest that the effects of 5HT might be partly attributable to its conversion to one or more of its deaminated metabolites. However, the effects of pargyline may not be entirely attributable to MAO inhibition since it also alters the CNS actions of 5HTA[5] and 5HTOL.

In rabbits pretreated with TETD, 5HT induced an immediate, marked reduction of the SNW ($38 \pm 15\%$ of control amplitude 2 min after injection; see Figure), a reversal of the early SNW enhancing effect of 5HT. Recovery began 5–10 min after injection, and 1 h after 5HT administration the SNW was less reduced than in animals not pretreated with TETD. In contrast, TETD did not significantly influence the effect of 5HIAA (Table). The reversal of the initial SNW enhancing effect of 5HT by TETD-inhibition of aldehyde dehydrogenase, together with the ability of high doses of 5HIAA to



Early effect of intraventricular serotonin (5HT) and 5-hydroxyindoleacetic acid (5HIAA, 0.03 mg) on averaged photic evoked responses. 50 responses added by Computer of Average Transients (analysis time 500 msec); negativity upwards. Voltage calibration 0.1 mV. Fine lines: control responses. Heavy lines: 2 min after injection of 5-hydroxyindoles. A and C: No pretreatment. B and D: Tetraethylthiuram disulfide (TETD) (250 mg/kg/i.p./24 h prior).

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Effect of intraventricular 5-hydroxyindoles on the amplitude of the slow negative wave of the photic evoked potential averaged by Computer of Average Transients (50 photic evoked potentials per record; analysis time 0.5 sec)

Pretreatment (mg/kg/i.p./24 h)	Treatment (mg intraventricular)	Minutes after injection		
		1–10	21–30	51–60
	CSF[a]	106.8 ± 6.9	97.0 ± 7.9	96.0 ± 8.4
	5HT 0.03	102.0 ± 8.9	65.9 ± 15.0	68.1 ± 14.7
	5HT 0.14	82.3 ± 17.2	68.0 ± 9.6	86.3 ± 9.8
	5HT 0.55	76.7 ± 14.7	81.0 ± 13.3	79.3 ± 4.6
	5HTOL 0.03	78.0 ± 14.7	52.3 ± 12.7	62.0 ± 15.8
	5HTOL 0.14	57.0 ± 8.4	67.8 ± 6.6	82.5 ± 12.0
	5HTOL 0.28	53.5 ± 3.9	56.5 ± 3.9	99.0 ± 14.1
	5HIAA 0.03	75.0 ± 13.6	68.0 ± 12.3	68.8 ± 12.7
	5HIAA 0.14	64.3 ± 8.6	85.5 ± 3.2	99.8 ± 6.9
	5HIAA 0.28	111.5 ± 13.6	125.0 ± 13.1	106.2 ± 10.8
Pargyline 100	5HT 0.03	106.0 ± 10.9	103.9 ± 14.4	105.6 ± 12.2
Pargyline 100	5HTOL 0.03	57.8 ± 17.6	54.5 ± 17.6	61.3 ± 19.2
Pargyline 100	5HIAA 0.03	74.8 ± 14.8	69.0 ± 12.7	69.4 ± 15.2
TETD 250	5HT 0.03	49.2 ± 12.1	66.8 ± 14.3	88.2 ± 21.6
TETD 250	5HIAA 0.03	84.9 ± 11.2	69.9 ± 9.6	78.8 ± 9.1

Slow negative wave amplitude (2 or more records per time interval) expressed as percentage of average control amplitude (10 control records obtained after 1 h habituation to flash stimuli). 4 or more non-anesthetized rabbits at each dose level. [a] Artificial cerebrospinal fluid.

induce a small increase in the SNW comparable to that observed with low doses of 5HT, may suggest that this enhancing effect of 5HT results in part from its conversion to 5HIAA. However, TETD inhibits many other enzymes, including dopamine-β-hydroxylase[8].

Discussion. The influence of pretreatment with a MAO inhibitor and an aldehyde dehydrogenase inhibitor on the effects of 5HT together with the effectiveness of 5HTOL and 5HIAA upon photic evoked potentials suggest that these deaminated metabolites may play a modulator role in serotonergic synapses within the optic pathway, in support of JOUVET's hypothesis[2] that a deaminated metabolite of 5HT triggers the pontogeniculate-optic cortex monophasic spikes of paradoxical sleep. The deaminated metabolites of 5HT have also been implicated in other CNS effects of 5HT[9–13, 14].

Resumen. El estudio de la curva dosis-respuesta demuestra que el 5-hidroxi-triptofol y el acido 5-hidroxi-indolacético son tan potentes como la serotonina en modificar las respuestas corticales ópticas en el conejo. Pretratamiento con pargilina o con disulfiram, dos inhibidores distintos del metabolismo de las neuroaminas, influenció marcadamente los efectos de la serotonina sin cambiar los efectos de sus metabolitos.

H. C. SABELLI and W. J. GIARDINA

Department of Pharmacology, The Chicago Medical School, 2020 West Ogden Avenue, Chicago (Illinois 60612, USA), 13 July 1970.

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Hemmung des durch blutdrucksenkende Pharmaka bei Ratten ausgelösten Trinkens durch Nephrektomie

Isoproterenol löst bei Ratten ein dosisabhängiges Trinken bei gleichzeitiger Antidiurese aus. Dieses Trinken ist durch den β-Rezeptorenblocker Propranolol hemmbar[1]. Neben anderen β-Sympathicomimetika führen auch Hydrazinophthalazine und die α-Rezeptorenblocker Phenoxybenzamin und Phentolamin zu verstärktem Trinken. Darüberhinaus liess sich das durch Hydralazine oder Phentolamin ausgelöste Trinken durch Bretylium oder Guanethidin verstärken und durch Propranolol hemmen[2].

FITZSIMONS et al.[3] und EPSTEIN et al.[4] konnten zeigen, dass Renin bzw. Angiotensin bei Ratten mit ausgeglichener Flüssigkeitsbilanz ebenfalls Trinken induzierten. Es erschien durchaus vorstellbar, dass die blutdrucksenkenden Pharmaka über eine Plasma-Reninsteigerung zum Trinken führen. Diese Reninsteigerung könnte einerseits durch die ausgelöste Hypotonie bedingt sein, andererseits durch Flüssigkeitsabstrom aus dem Gefässraum in das Gewebe. Tatsächlich führen Isoproterenol, Phentolamin und Hydralazin in den zum Trinken führenden Dosen zu einer Steigerung der Plasmareninaktivität (PRA)[5].

Ähnlich wie das Trinken liess sich die durch Hydralazin oder Phentolamin ausgelöste Steigerung der PRA durch Bretylium oder Guanethidin potenzieren und durch