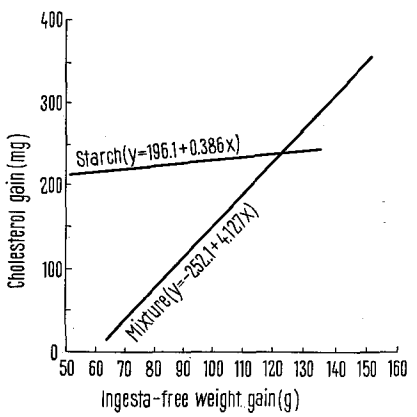
Table III. Comparison of mean caloric intakes and serum cholesterol levels as influenced by dietary carbohydrate source and forced exercise

Carbohydrate source	Caloric intake		Serum cholesterol	
	Exercised (kcal/day)	Sedentary (kcal/day)	Exercised (mg/100 ml)	Sedentary (mg/100ml)
Starch	41.0 ± 2.5[a]	38.7 ± 2.2	48.0 ± 6.0	89.0 ± 32.4
Mixture	45.3 ± 2.7	43.1 ± 3.4	78.0 ± 27.0	78.6 ± 13.8

[a] Standard error of the mean.

Conclusion. Weanling, male rats were fed diets where the carbohydrate source was provided either by starch or a mixture of carbohydrates similar to that found in U.S. 'market basket' diets. Half the animals were forced to exercise by 15 min of treadmill running daily. Tissue cholesterol accumulation in the rats fed only starch was unrelated to weight gain, but in those fed the mixture of carbohydrates the tissue cholesterol gain was highly weight gain dependent.



Regression lines of body cholesterol gain vs. ingesta-free body weight gain as influenced by dietary carbohydrate sources. Moderate forced exercising by treadmill running (15 min/day) had no effect on this regression, and hence each line represents 10 observations. The linear regression equation is indicated for each line.

Zusammenfassung. Drei Wochen alte männliche Ratten wurden auf eine Diät gesetzt, aus der die Kohlehydratquelle entweder aus Stärke oder einer Mischung von Kohlehydraten, die dem U.S.-Ernährungsstandard gleicht, bestand. Die Cholestrolansammlung im Gewebe der Ratten, denen nur Stärke gefüttert wurde, stand nicht in Verbindung mit der Gewichtszunahme; dagegen stand die Cholestrolzunahme im Gewebe jener Ratten, die mit einer Mischung von Kohlehydraten ernährt wurden, in direktem Zusammenhang mit der Zunahme in Gewicht.

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Optic Evoked Potential Changes Induced by Deaminated Metabolites of Serotonin: 5-Hydroxytryptophol and 5-Hydroxyindole Acetic Acid

Although monoamine oxidase (MAO) has been considered the 'cholinesterase' of serotonin (5HT), many of the effects of this amine or of its precursor, 5-hydroxytryptophan (5HTP), are prevented or 'reversed' rather than enhanced by MAO inhibition: enhancement of carbohydrate metabolism[1], protection against radiation[2], sleep induction in newly hatched chicks[3,4], enhancement of slow photic evoked potentials[5], etc. Among other alternatives, it is possible that part of the effect of 5HT be indirect, i.e., mediated by the formation of one or more of its deaminated products: 5-hydroxyindoleacetaldehyde (5-hydroxytryptaldehyde, 5HTA), 5-hydroxytryptophol (5HTOL) or 5-hydroxyindole acetic acid (5HIAA). We have shown that 5HTA and tryptaldehyde (3-indoleacetaldehyde) mimic the effects of 5HT and tryptamine on rabbit photic evoked potentials[5,6] and on sleep induction in newly hatched chicks[4]. 5HTOL may intervene in the control of the secretion of luteinizing hormone in rats[7].

There is also biochemical evidence for a physiological significance of 5HT deaminated products: (a) The incorporation of radioactivity into the acid-insoluble fraction of brain homogenates from labeled 5HT or 5HTP is blocked by MAOI's[8,9]. (b) The reduction of 5HTA to

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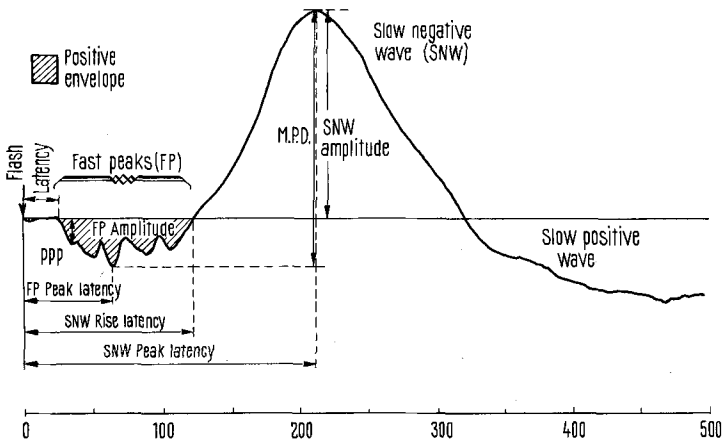

Fig. 1. Optic cortex potential evoked by 10 μsec red flash (Kodak Wratten Filter 92). This and following Figures: Negativity upwards. 50 responses added by Computer of Average Transients. Analysis time: 500 msec. PPP, primary positive potential; MPD, maximal potential deflection. Note the baseline drawn at the mid-level of the EEG during the first 20 msec after the flash.

5HTOL is markedly increased by alcohol[10] probably because acetaldehyde inhibits its oxidation to 5HIAA. (c) The removal of 5HIAA from the brain and the cerebrospinal fluid (CSF) is dependent on an active transport system which can be inhibited with probenecid[11,12].

There is no a priori reason to consider 5HTOL and 5HIAA as inert metabolites, particularly when they are formed near the chemically sensitive synaptic areas. In this paper we show that both 5HTOL and 5HIAA exert effects upon the photic evoked potential closely resembling those of 5HT in both direction and magnitude. This preparation was selected because the optic pathway appears to be one of the sites of action of 5HT[13,14,15].

Materials and methods. The experimental procedure for monopolar recording of the photic evoked potential in non-anesthetized rabbits, which is standard in our laboratory, has been described elsewhere[16]. Figure 1 indicates the procedures followed in the analysis of evoked potential records 'averaged' by C.A.T. Drugs were administered in the lateral ventricle ipsilateral to the recording site, dissolved in 0.2 ml of artificial CSF (glucose 3.5 m*M*; NaCl 146 m*M*; KCl 2.7 m*M*; $MgCl_2$ 5.4 m*M*; Ca Cl_2 5.4 m*M*). All drugs were commercially obtained.

Results. Figure 2 summarizes some of the effects of equal doses of 5HT, 5HTOL and 5HIAA. All 3 agents decreased to the same extent the amplitude of the slow negative wave (SNW) immediately after injection and this depression lasted for more than 1 h (Figure 1A). The latency to the peak of the SNW was also shortened by all 3 drugs. The changes were small but there was a good direct correlation between the time courses of the reduction in amplitude and the shortening in latency of the SNW, regardless of the treatment. Thus, maximal effects occurred at 5 min with 5HTOL ($54 \pm 11\%$ amplitude, $80 \pm 2\%$ latency) and 5HIAA ($59 \pm 9\%$ amplitude, $94 \pm 5\%$ latency) and at 15 min with 5HT ($63 \pm 14\%$ amplitude, $93 \pm 3\%$ latency). The latency to the rise of the SNW was initially shortened by 5HT (16%) and slightly shortened (10%) for more than 1 h by 5HTOL; no significant changes were observed with 5HIAA. 5HIAA markedly reduced the duration of the SNW (Figure 4). Note also the shortening of SNW peak latency (Figure 4, C–F), which is shorter than the minimal latency observed in control records (Figure 4 B).

The maximal amplitude of the positive fast potential (Figure 1B) was slightly reduced for more than 15 min after 5HT administration. 5HTOL and 5HIAA reduced the amplitude of the positive fast potential much more than 5HT ($67 \pm 18\%$ with 5HTOL, $79 \pm 12\%$ with 5HIAA 5 min after injection). Latency to the maximal positive fast potential was initially shortened by 5HTOL (Figure 3c), whereas 5HT prolonged it slightly; in MAOI animals, 5HT (0.03 mg) shortened this latency[5]. Similar shortening has not been observed with 5HTA or with 5HIAA.

Discussion. The present experiments show that 5HIAA and 5HTOL are biologically active at a dose level commonly used to demonstrate similar effects of 5HT administered i.v.[15,17]; we have previously studied the effects of a wide range of doses (0.03–1.0 mg) of intraventricular 5HT upon photic evoked responses in non-anesthetized rabbits[5]. The reduction of the slow negative component observed with intraventricular 5HT at the

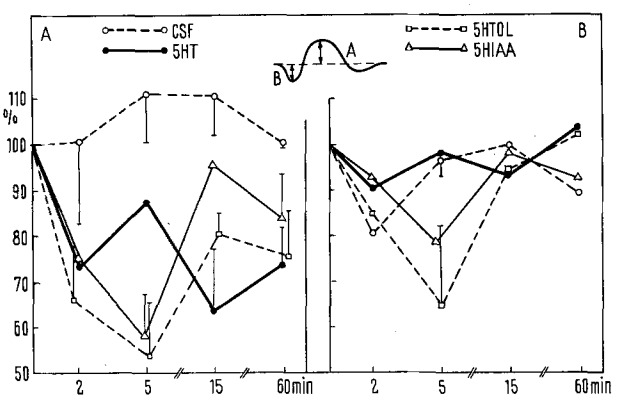

Fig. 2. Percentage changes in amplitudes of fast positive peak (A) and slow negative wave (B). 5HT, serotonin; 5HTOL, 5-hydroxytryptophol; 5HIAA, 5-hydroxyindole acetic acid. All drugs: 0.14 mg in 0.2 ml of CSF (cerebrospinal fluid). Standard errors drawn only for significant drug effects and the corresponding CSF controls.

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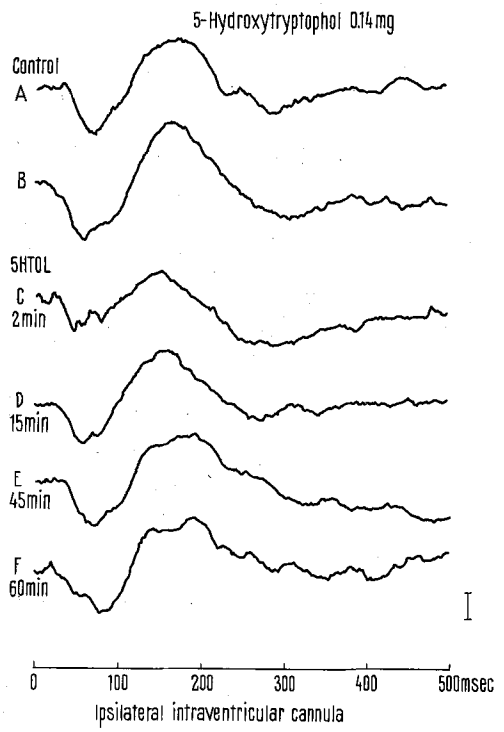

Fig. 3. Effect of 0.14 mg 5-hydroxytryptophol (5HTOL) on optic cortex potentials evoked by red flash. A, control after 60 min habituation to flash.

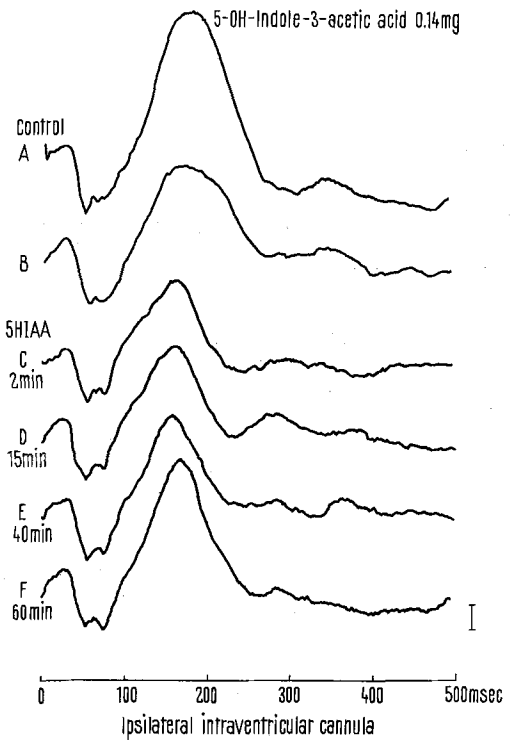

Fig. 4. Effect of 0.14 mg 5-hydroxyindole acetic acid (5HIAA). See Figure 3.

dose used in this study resembles that obtained with usual doses of systemically administered 5HTP. Fast potentials, however, were modified in different ways by the amino acid, the amine, the aldehyde[6], the alcohol and the acid members of the 5HT series.

The demonstration of pharmacological effects with exogenous administration of these compounds does not imply that the corresponding endogenous products of 5HT metabolism play a physiological role in brain. However, in view of the presence and biological activity of these substances and the additional evidence that MAOI's prevent part of the effects of 5HT and of 5HTP, there is no reason to dismiss them as inert metabolites; direct experimental evidence will be required in each instance to demonstrate or to rule out a neural function.

A current concept of neuroamine modulation of synaptic transmission is modeled after our knowledge of acetylcholine mediation at the neuromucular junction. Among other concepts borrowed from this peripheral model, a precursor role is attributed to the amino acid and a modulator function to the amine, and the deaminated products are considered as inactive metabolites. This model may not be applicable to neuroamine mediation in view of the slow time course of the response and the ability of the amines to act upon depolarized cells, at least in the case of smooth muscle[18]. The biological activity of 5HTA[6,4], 5HTOL, 5HIAA and melatonin in addition to the possible direct effects of 5HTP (independent of its conversion to 5HT) suggest the concept of a 'modulator chain', each member of which plays a physiological role presynaptically, postsynaptically, or both. The formation of 5HTOL or of 5HIAA represent alternative metabolic pathways for 5HTA probably controlled by localized alteration in the redox environment[19]. In the adrenergic series, dopamine, norepinephrine, epinephrine and possibly DOPA function as modulators; however, insofar as we know, the 3 amines play such a physiological role at different sites and do not act in conjunction at the same synapse. Other pairs of active compounds are histamine-methylhistamine[20] and glutamic acid-GABA[21].

Indolacetaldehyde and 5HIAA are known to be plant hormones[22]. PULLMAN and PULLMAN[23] pointed out that the electronic configuration requirements for biological function are so stringent that the same limited number of chemicals is used all over the plant and animal kingdoms to accomplish a variety of functions[24].

Resumen. En el conejo no anestesiado, el acido 5-hidroxiindoleacético y el 5-hidroxitriptofol modifican los potenciales ópticos evocados de manera similar que la serotonina. Los derivados deaminados de la serotonina probablemente modulan las sinápsis serotonérgicas.

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