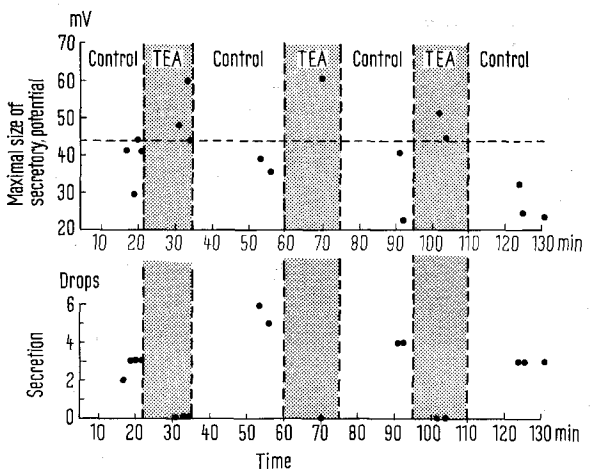

Maximal sizes of secretory potentials (the difference between the maximal level of the membrane potential after stimulation and the resting membrane potential) and secretion as a function of time after start of perfusion in experiment No. 39.

Table I. Maximal sizes of secretory potentials in mV during perfusion with control and TEA Locke solutions

Experiment No.	Control (*n*)	TEA (*n*)	*t*-test
28	37.6 (3)	39.2 (5)	–
37b	23.2 (6)	31.6 (3)	–
38b	31.6 (5)	44.6 (5)	–
39	34.2 (11)	51.6 (6)	–
Total	31.4 ± 1.6 (25)	43.3 ± 2.5 (19)	$p < 0.001$

Table II. Maximal sizes of secretory potentials in mV during perfusion with control and potassium-free Locke solutions

Experiment No.	Control (*n*)	Potassium-free (*n*)	*t*-test
29	27.2 (4)	28.0 (7)	–
35	23.8 (7)	31.0 (7)	–
36	23.0 (4)	29.0 (4)	–
37a	21.7 (3)	32.5 (6)	–
38a	28.3 (4)	42.0 (4)	–
Total	24.8 ± 1.0 (22)	32.2 ± 1.3 (28)	$p < 0.001$

potassium-free solution were significantly greater than the sizes of those recorded during perfusion with control Locke solution.

Discussion. During perfusion with a 10 m*M*[5] or a 20 m*M*[4] potassium Locke solution, the sizes of the secretory potentials were significantly diminished compared with those recorded during perfusion with control Locke solution. Thus the size of the secretory potential seems to depend on the size of the potassium equilibrium potential across the basal acinar cell membrane. The results obtained with the low sodium TEA solution suggest that the outward potassium current is normally followed by an inward sodium current. In the rat submandibular gland, the acinar secretory potential may either consist in a hyper- or depolarization[6]. The difference between these secretory potentials and those found in the cat[1,7,8] and dog[4] may only be due to different sizes of the sodium and potassium currents, the sodium current being the most important in the depolarizing cells and the potassium current dominating in the hyperpolarizing acinar cells. This concept agrees well with the recent finding[9] that dinitrophenol in a concentration sufficient to inhibit salivary secretion and active uptake of potassium into the gland has no effect on the size of the secretory potentials if the gland has not lost too much potassium.

Zusammenfassung. Während der Perfusion der Submandibulardrüse der Katze mit kaliumfreier Lockelösung oder mit einer Lockelösung, in der das meiste Kochsalz durch Tetraethylammoniumchlorid ersetzt wurde, sind die sekretorischen Potentialdifferenzen der basalen Azinuszellmembran vergrössert. Ein Kaliumstrom aus der Azinuszelle, der teilweise von einem Natriumstrom in die Zelle kurzgeschlossen wird, könnte die sekretorischen Potentialdifferenzen erklären.

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A Histamine-Dependent Increase of 5-Hydroxytryptamine in the Rat Brain in vivo

In a previous report[1] we have produced evidence suggesting that the cerebral acetylcholine, released during central nervous system stimulation, is triggering a mechanism to induce an enhancement of the rate of synthesis of histamine in the rat brain. The present data show that the increase of cerebral histamine during central nervous system stimulation is in turn inducing an increase in cerebral 5-hydroxytryptamine.

Material and method. Albino rats of either sex, 70–120 g of body weight, were placed in individual wooden cages (9 × 4 × 5 inches) provided with a copper wired grid bottom connected to an electronic stimulator. Electrical stimulation was applied to the paws of the rat over a period of 5 min, 8 c/sec, 20 msec duration, and over a period of 30 min, 4 c/sec, 20 msec duration. A voltage was employed high enough to cause a discrete continuous jumping of the animal. At the end of the stimulation period, the rats were sacrificed by decapitation, the brains were removed as soon as possible (less than 3 min) and the cerebral hemispheres and brain stem homogenized in ice-cold acid ethanol. After extraction, histamine and 5-hydroxytryptamine were separated by descending paper chromatography using Whatman paper No. 1 and a solvent system of isopropanol–0.1 *N* HCl: 7:3. Chromatograms were run for 18 h at room temperature and the eluates assayed in the guinea-pig ileum and the rat stomach respectively. Specific antagonists were employed.

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Changes in the levels of histamine and 5-hydroxytryptamine in the rat brain under various conditions

Treatment[a]	Histamine		5-hydroxytryptamine	
	Cerebral hemispheres	Brain stem	Cerebral hemispheres	Brain stem
	(μg/g of fresh tissue, Mean $\pm$ S.E.[b])			
Controls (14)	1.74 ± 0.08	1.87 ± 0.06	0.34 ± 0.01	0.41 ± 0.02
Elect. stim. 5 min (8)	2.48 ± 0.09 (+43)	2.59 ± 0.05 (+39)	0.43 ± 0.02 (+26)	0.58 ± 0.01 (+41)
Parathion (7)	2.42 ± 0.05 (+39)	2.51 ± 0.06 (+34)	0.42 ± 0.01 (+24)	0.56 ± 0.01 (+37)
Parathion + Elect. stim. 5 min (8)	3.60 ± 0.21 (+107)	4.09 ± 0.28 (+119)	0.87 ± 0.08 (+156)	1.11 ± 0.10 (+171)
L-Histidine (7)	2.03 ± 0.10[c] (+17)	2.56 ± 0.11 (+37)	0.45 ± 0.04 (+32)	0.60 ± 0.03 (+46)
Parathion + L-Histidine (7)	4.05 ± 0.14 (+133)	4.88 ± 0.15 (+161)	0.72 ± 0.10 (+112)	0.94 ± 0.10 (+129)
Elect. stim. 30 min (6)	3.25 ± 0.05 (+86)	3.33 ± 0.05 (+78)	0.84 ± 0.02 (+147)	1.05 ± 0.02 (+156)
α-m-Histidine (8)	1.42 ± 0.04 (—18)	1.56 ± 0.07 (—17)	0.32 ± 0.02[d] (—6)	0.44 ± 0.03[d] (+7)
α-m-Histidine + Elect. stim. 30 min (8)	1.35 ± 0.04 (—22)	1.50 ± 0.04 (—20)	0.35 ± 0.02[d] (+3)	0.45 ± 0.01[d] (+10)
L-Tryptophan (8)	1.65 ± 0.07[d] (—5)	1.87 ± 0.07 (00)	0.88 ± 0.02 (+159)	0.97 ± 0.04 (+137)

[a] For schedules and dosages see text. [b] In brackets under treatment, number of experiments. Other numbers in brackets, percent change of controls. All values for treated groups are different from controls, $P < 0.01$, except where indicated. [c] Different from controls, $P < 0.05$. [d] Not different from controls, $P > 0.05$.

The histamine purification included boiling the eluate. Moreover, incubation with chymotrypsin and determination of the melting point of the picrate derivative obtained from pooled eluates were also carried out. Recoveries were over 65% for amounts added to sample homogenates in the range of concentrations studied. Drugs used for treatments added to sample homogenates did not interfere with the procedure. Further details will be published elsewhere as part of a multi-assay technique[2].

Results and discussion. The electrical stimulation for 5 min induces a significant increase in histamine and 5-hydroxytryptamine both in the cerebral hemispheres and brain stem of the rat (Table). When parathion, a cholinesterase inhibitor[3], is administered, 0.2 mg/kg i.p., 30 min before sacrifice, the brain histamine significantly increases, and this is accompanied by a significant increase of the brain 5-hydroxytryptamine. The physiologically released cerebral acetylcholine might be accumulated because of the cholinesterase inhibition and enhancing this way the synthesis of histamine[1] and 5-hydroxytryptamine, since the latter amine hardly traverses the blood-brain barrier[4,5]. These effects are much better observed when parathion is combined with electrical stimulation for 5 min, when presumably more acetylcholine is released[6]. The cerebral acetylcholine might be simultaneously speeding the synthesis of histamine and 5-hydroxytryptamine or the increase of one amine would be inducing the increase of the other. When L-histidine, the precursor of histamine is administered, 1000 mg/kg i.p. 60 min before sacrifice, both the cerebral histamine and 5-hydroxytryptamine increase significantly. Moreover, when the synthesis of histamine from L-histidine is enhanced through the protection of acetylcholine with parathion[1], there is also a larger increase of 5-hydroxytryptamine. This suggests that, under our experimental conditions, the increase of brain 5-hydroxytryptamine depends on the increase of brain histamine.

Electrical stimulation for 30 min induces marked increments of both amines in the brain. Administration of α-methyl-histidine, a specific inhibitor of histidine decarboxylase[7], at the dose of 120 mg/kg i.p. 60 min before sacrifice, induces a significant depletion of the brain histamine with no change in the levels of 5-hydroxytryptamine. Previous administration of α-methyl-histidine blocks the outstanding increments of both amines induced by the electrical stimulation applied over a period of 30 min. This finding gives further support to the assumption that the 5-hydroxytryptamine increase depends on the histamine increase in the brain during central nervous system stimulation. Administration of L-tryptophan, 600 mg/kg i.p. 60 min before sacrifice, induces a marked increase of cerebral 5-hydroxytryptamine with no change in histamine, which suggests that the relationship between the changes of histamine and 5-hydroxytryptamine works only in one direction. From this and the previous report[1], a sequence of events can be established for acetylcholine, histamine and 5-hydroxytryptamine in the cerebral hemispheres and brain stem of the rat, under our experimental conditions, during central nervous system stimulation. This sequence can be schematized as follows: ACh → HIST. → 5-HT.

Résumé. Pendant l'excitation du systeme nerveux central du rat, on constate une augmentation de l'histamine et de la sérotonine cérébrales. L'augmentation de la sérotonine dépend de celle de l'histamine.

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