Effect of Theophylline on Acid Secretion of Stimulated Human Gastric Mucosa

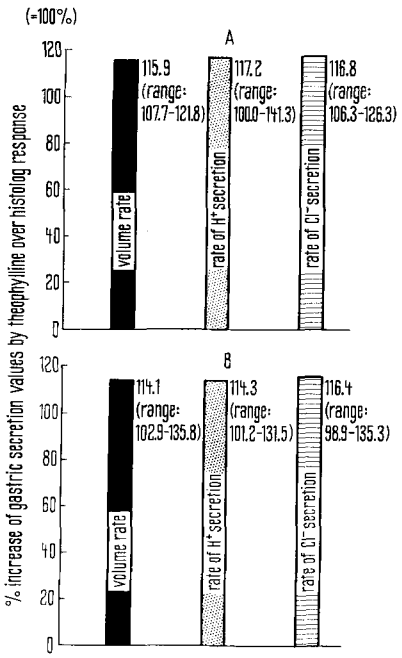
From studies on sodium transport in the toad bladder the role of cyclic 3′, 5′-AMP(adenosine-3′, 5′-phosphate) as a naturally occurring intracellular mediator of the action of a variety of hormones in responsive organs was first suggested by ORLOFF and HANDLER[1]. This constituent is capable of enhancing various physiological functions in a number of tissues, including liver, muscle, thyroid, adrenal gland, and adipose tissue[2–4]. ACTH[5], glucagon[2], ADH(vasopressin)[1,6–8] and parathyroid hormone[9] have in common the property of stimulating the production of cyclic 3′, 5′-AMP by increasing the activity of the enzyme adenyl cyclase, which is probably located in the cell membrane[10]. Cyclic 3′, 5′-AMP alters the activity of enzymes within the receptor tissues, finally yielding the physiologically recognizable effect of the hormone[1]. On the other hand, a critical increase in the concentration of cyclic 3′, 5′-AMP may be effected by inhibition of its degradation to inactive adenosine-5′-phosphate(5′-AMP). This reaction is catalyzed by cyclic nucleotide phosphodiesterase[2], enhanced by imidazole and inhibited by methyl xanthines, like theophylline and caffeine[11,12].

It has been shown that theophylline and cyclic 3′, 5′-AMP mimic the effects of ADH on short-circuit current and osmotic water flow across toad bladder[1]. ADH and theophylline have a synergistic effect on the concentration of cyclic 3′, 5′-AMP[13]. Cyclic 3′, 5′-AMP is involved, too, in insulin secretion, which can be stimulated by theophylline[14]. We became interested in theophylline after observing that methyl xanthines stimulate acid secretion and respiration in the frog (*Rana pipiens*) gastric mucosa in vitro[15]. Furthermore, an increase in short-circuit current was observed when either ADH, theophylline or cyclic 3′, 5′-AMP was added to the serosal surface of isolated rabbit ileal mucosa[16]. In this paper, the effect of theophylline on acid secretion of human gastric mucosa during submaximal and maximal stimulation with histalog was examined.

Methods and materials. Experiments were carried out on 8 men and 3 women ranging in age from 20–41 years. 8 persons had a normal, 3 a subnormal secretory ability of gastric acid. After fasting overnight, a double-balloon-tube – proofing both cardia and pylorus – was passed through the mouth and placed into the stomach, under X-ray control. For an accurate collection of gastric juice the subjects were placed in the left lateral decubitus position. The residual gastric content was aspired and discarded. Basal secretion was collected for 20 min. Thereafter the stimulant drug was i.v. infused at a constant rate for 100 min and collections were continued at 20 min intervals. Gastric contents were aspired manually continuously with a syringe during the time of the test. In addition, repeated air insufflations were performed by syringe. In 5 persons the primary stimulus was submaximal by constant i.v. infusion of 50 mg histalog (betazole hydrochloride Lilly®) per hour. In the remaining 6 subjects maximal acid secretion was evoked by i.v. infusion of 2 mg histalog/kg body weight/h[17]. 60 min after the start of the infusion we injected 2 ampoules of Cordalin Homburg® (= 340 mg 7-(β-hydroxyethyl)-theophylline plus 100 mg theophylline) i.v. in each case and continued the test for additional 40 min.

From each specimen of gastric juice, the volume rate was measured in ml/min and the concentration of hydrogen ions determined by titrating a sample of juice with n/10 NaOH to a pH of 7.0 using a micro-glass electrode and the potentiometer E 353 Metrohm AG, Herisau, Switzerland. For chloride analyses we used the method of SCHALES and SCHALES[18]. Osmotic pressure in plasma and gastric juice was measured by a semiautomatic osmometer (Dr. H. Knauer, Berlin 33).

Results and conclusions. During submaximal and even during maximal stimulation of gastric acid output with histalog, theophylline was capable of enhancing the secretory rates of both hydrogen ions and chloride



Per cent changes of the rates of gastric secretion by i.v. injection both of 340 mg 7-(β-hydroxyethyl)-theophylline and 50 mg theophylline during submaximal and maximal acid secretory response to histolog in 11 subjects. (A) During submaximal stimulation of gastric acid secretion with 50 mg histolog/h i.v. infused. (B) During maximal stimulation of gastric acid secretion with 2 mg histolog/kg body weight/h, i.v. infused.

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significantly, as shown in the Figure. The rise in acid output was due to a significant increase of the volume rate of gastric secretion. There was no significant change of the concentrations of hydrogen ions and chloride in gastric juice after injection of theophylline. Under such conditions osmotic concentration ratio between gastric secretion and plasma was similar to the control values and did not exceed the limiting level of 1.0[19]. Upon stimulation the osmolality of gastric juice increases and in the normal stomach at maximum equals that of the plasma. In comparison with this finding, the effect of histalog on the concentrations both of hydrogen ions and chloride in gastric juice can be augmented by combining it with atropine[17]. As a result, previously obtained isotonic secretion will become hypertonic to plasma. This is, however, the only condition at present known, under which hypertonic gastric juice can be obtained. A complete description of these findings together with additional investigations to elucidate the mechanism of action of theophylline on gastric acid production will be presented elsewhere[20]. The possibility that cyclic 3′,5′-AMP participates on a molecular basis in the secretory mechanism of gastric acid merits further investigation. The true nature of structural alterations and the biochemical pathway involved in this process are still unknown[21].

Zusammenfassung. Während submaximaler und maximaler Säurestimulation mit Histalog steigert i.v. Injektion von 340 mg 7-(β-Hydroxyäthyl)-theophyllin und 100 mg Theophyllin (= «OT Homburg») beim Menschen die Magensalzsäurebildung signifikant durch Zunahme der Volumenrate. Die Befunde werden im Hinblick auf die mögliche Bedeutung von zyklischem 3′,5′-AMP als intrazelluläre Mittlersubstanz bei der Bildung und Sekretion von Magensalzsäure diskutiert.

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Note sur l'innervation des branchies chez *Anguilla anguilla* L.

De nombreux travaux morphologiques ont décrit la structure des organes de la respiration aquatique chez les poissons Téléostéens. Ces contributions ont permis d'expliquer plusieurs phénomènes physiologiques observés au niveau des aires vasculaires et des tissus constituant les branchies. Plus particulièrement, les renseignements rassemblés par Vialli[1], Hughes et Grimstone[2] et puis par Newstead[3] confirment les plus anciennes observations de Biétrix[4] relatant l'existence d'un système contractile associé aux cellules du pilastre.

Récemment, Gilloteaux[5,6] a montré l'intérêt de la technique de fixation-coloration de Maillet appliquée aux Invertébrés. Celle-ci fut utilisée avec succès sur les branchies de l'Anguille. Rapprochant ces résultats de ceux recueillis par Laurent et Dunel[7] à propos de l'innervation de la pseudobranchie chez divers Téléostéens, nous avons remarqué des fibres nerveuses et des corps neuroniques parmi les tissus formant les feuillets branchiaux (Figure 1). Des prolongements nerveux aboutissent à la paroi des artérioles afférentes et efférentes. A la hauteur des fibres musculaires adductrices, nous avons relevé de nombreuses jonctions neuro-musculaires en anneau (Figure 2). Les cellules piliers situées à la base des lamelles sont fréquemment entourées par des faisceaux de prolongements issus de neurones bi- et multipolaires (Figures 3 et 4).

Compte tenu de ces observations, il nous semble possible de penser qu'une régulation nerveuse produirait

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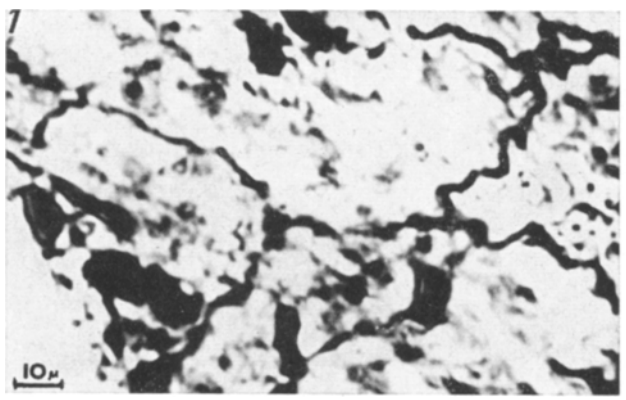

Fig. 1. Neurones et prolongements situés dans l'arête branchiale (Maillet).

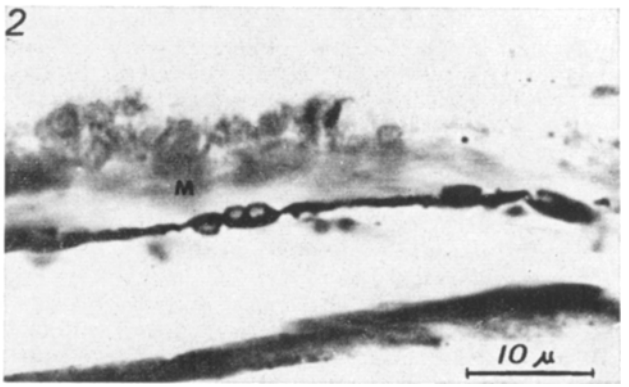

Fig. 2. Jonctions neuro-musculaires en anneau; M, fibre musculaire de l'adducteur des filaments branchiaux (Maillet).