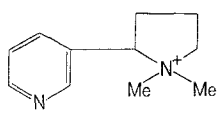
The Chronic Effects of Nicotine Monomethiodide on Gastric Secretion in Pylorus-Ligated Rats

Nicotine increases gastric secretion in rats when given daily in a dose of 1000 μg/kg[1]. We have recently shown that this effect is mediated via anterior hypothalamic nuclei and the vagus nerves[2-4]. Reported here are the chronic effects of nicotine monomethiodide (I) on gastric secretion in pylorus-ligated rats. Nicotine monomethiodide is a quaternary salt of nicotine which does not cross the blood brain barrier[5,6].

[I]  I^-

Materials and methods. 24 male Sprague-Dawley rats[7] weighing 322.2 ± 4.7 g were used. They were fed and housed as described previously[8] and randomly divided into 2 groups of 12 rats each. The rats were injected s.c. daily for 14 days with nicotine monomethiodine (Group 1) or NaCl (Group 2).

Nicotine monomethiodide was prepared as described previously[9-11] and was a generous gift from Professor BARLOW. For injection it was prepared in 6.0 g/100 ml gelatin (pH 5.20, 24 °C) in a concentration of 1000 μg/ml. Rats in Group 2 received 0.85 g/100 ml NaCl in 6 g/100 ml gelatin (pH 4.30, 25 °C).

After 14 days of injections the rats were isolated from food for 40 h as described previously[8]. Basal gastric secretion was collected after ligation of the pylorus under ether anesthesia[1,8]. After 2 h of pylorus-ligation the animals were decapitated without further anesthetic exposure, and the gastric juice collected and analyzed as described previously[1,8]. The brain was rapidly removed from the skull and split sagitally into 2 equal portions. One half was assayed for choline, acetylcholine and nicotine concentrations, whereas the second half was used for estimating acetylcholinesterase activity. Choline, acetylcholine and nicotine were assayed by gas chromatography after N-demethylation with sodium benzenethiolate. Choline and acetylcholine were assayed as described previously[12]. After the internal standard had eluted from the column the temperature was raised to 165 °C. At this temperature nicotine eluted at 8 min. Acetylcholinesterase activity was determined as follows: One half of each brain was homogenized in 0.9% NaCl with a teflon homogenizer to form a 10% homogenate. After activation with Triton X-100, 1.0 ml of each homogenate was assayed for acetylcholinesterase activity by constant pH titration at pH 7.4 and 30 °C with 3 m*M* acetylcholine as substrate. A Radiometer automatic titrator was used with a total volume of 20.0 ml 0.9% NaCl[13].

Results. Gastric secretory data are presented in Table I. There were no differences between control and nicotine monomethiodide-treated rats for any parameter. Similarly, there were no differences in mean choline and acetylcholine levels, or mean acetylcholinesterase activity between the 2 groups of rats (Table II), and no nicotine was detected in the brain (Table II).

Discussion. Nicotine when given acutely to rats produces either no alteration in gastric secretion or secretory depression[14,15]. On the other hand, when given daily for 14 days, nicotine has been shown to increase gastric secretion by a mechanism involving the anterior hypothalamus and the vagus nerves[3,4]. The absence of activity in this experiment with nicotine monomethiodide, a quaternary salt of nicotine which does not cross the blood brain barrier, supports previous findings implicating a central mechanism in chronic nicotine-induced gastric secretory stimulation.

1 J. H. THOMPSON, C. A. SPEZIA and M. ANGULO, Experientia *26*, 615 (1970).
2 J. H. THOMPSON and M. ANGULO, Experientia *27*, 404 (1971).
3 J. H. THOMPSON, R. GEORGE and M. ANGULO, Proc. West. Pharmac. Soc. *14*, 173 (1971).
4 J. H. THOMPSON and R. GEORGE, Am. J. dig. Dis. *17*, 513 (1972).
5 A. GOLDSTEIN, L. ARONOW and S. M. KALMON, *Principles of Drug Action* (Hoeber Medical Division, Harper and Row, New York 1968), p. 772.
6 I. GELLER, R. HARTMANN and K. BLUM, Psychopharmacologia *20*, 355 (1971).
7 Charles River Breeding Laboratories, Breeding Shed 1, North Wilmington, Massachusetts, USA 01887.
8 J. H. THOMPSON, C. A. SPEZIA and M. ANGULO, Res. Commun. Chem. Path. Pharmac. *1*, 230 (1970).
9 R. B. BARLOW and N. A. DOBSON, J. Pharm. Pharmac. *7*, 27 (1955).
10 R. B. BARLOW and N. A. DOBSON, J. Pharm. Pharmac. *7*, 296 (1955).
11 R. B. BARLOW and J. T. HAMILTON, Br. J. Pharmac. *18*, 543 (1962).
12 D. J. JENDEN, R. A. BOOTH and M. ROCH, Analyt. Chem., *44*, 1879 (1972).
13 J. JENSEN-HOLM, H. H. LAUSEN, K. MILTHERS and K. O. MØLLER, Acta pharmac. tox. *15*, 384 (1959).
14 J. H. Thompson, Am. J. dig. Dis. *15*, 209 (1970).
15 J. H. THOMPSON and W. BRÜCKNER, Europ. J. Pharmac. *9*, 261 (1970).

Table I. Gastric secretion following nicotine monomethiodide

Parameter	*N*	NaCl control	*N*	Nicotine/monomethiodide	*P*
Gastric juice volume (ml/2 h)	12	2.5 ± 0.27	12	2.8 ± 0.34	ns
Gastric juice volume/100 g (ml/100 g/2 h)	12	0.77 ± 0.08	12	0.86 ± 0.11	ns
Acid concentration (mEq/l)	12	83.4 ± 6.2	12	79.8 ± 7.1	ns
Acid output (μEq/100 g/2 h)	12	64.0 ± 8.2	12	64.1 ± 7.0	ns
Pepsin concentration (mg/ml)	12	0.62 ± 0.04	12	0.52 ± 0.04	ns
Pepsin output (mg/2 h)	12	1.49 ± 0.15	12	1.37 ± 0.15	ns
Sodium (mEq/l)	12	57.3 ± 4.3	12	57.9 ± 4.3	ns
Potassium (mEq/l)	12	39.2 ± 3.6	12	34.8 ± 4.6	ns
Chloride (mEq/l)	12	102.1 ± 4.2	12	101.3 ± 4.7	ns
Osmolarity (mOsm/kg water)	12	284.2 ± 16.8	12	293.3 ± 19.4	ns

Data are reported as mean value ± S.E.M. for 12 rats per group. *P*-values are all non-significant.

Table II. Brain levels of choline, acetylcholine, acetylcholinesterase and nicotine following nicotine monomethiodide

	NaCl control	Nicotine monomethiodide	P
Choline (nmoles/g)	37.10 ± 5.37	42.71 ± 6.52	ns
Acetylcholine (nmoles/g)	12.81 ± 0.76	13.50 ± 0.77	ns
Acetylcholinesterase (μmoles/min/g)	8.66 ± 0.10	8.88 ± 0.24	ns
Nicotine (μg/g)	0	0	ns

Data are reported as mean values ± S.E.M. for 6 rats

Additional effects of acute nicotine administration on gastro-duodenal function have recently been reported. KONTUREK et al.[16] have shown that nicotine reduced pancreatic bicarbonate output, and ROBERT et al.[17] that nicotine increased ulcer formation in rats given synthetic gastrin and carbachol. It remains to be seen whether these effects are also produced by nicotine monomethiodide.

As far as peripheral activity goes, nicotine monomethiodide produces cardiovascular effects in spinal cats comparable with those of nicotine hydrogen tartrate[9]. For example, BARLOW and DOBSON[9] reported that nicotine monomethiodide was at least as active as, if not more active than nicotine hydrogen tartrate, and that the responses could be abolished by prior treatment with hexamethonium. However, the action of the two compounds may be somewhat different since the shape of the blood-pressure response to the two drugs was different, and it was impossible to produce complete blockade of sympathetic ganglia with nicotine monomethiodide.

Based upon intraventricular injections of nicotine and the choline ester carbachol in cats, ARMITAGE and HALL[18] found that carbachol had two actions, one of which resembled that of nicotine. The nicotine-like effect was potentiated by cholinesterase inhibitors and prevented by hemicholinium, in agreement with the hypothesis that nicotine acts centrally by releasing acetylcholine. Mean concentrations of choline and acetylcholine in the brain did not differ significantly from previously published normal values[19]. This is not surprising since nicotine monomethiodide does not cross the blood brain barrier. It is theoretically possible that some nicotine monomethiodide could be converted within the body to a non-quaternized form, which could then cross the blood brain barrier. However, no nicotine or nicotine methiodide was detected in brain tissue by a method with a sensitivity of 8.0 ng/g brain[20].

Résumé. L'action de la nicotine monométhyliodine (NMI) sur la sécrétion gastrique basique et sur les concentrations de choline de cervelles, d'acétylcholine et de nicotine et sur l'activité de la transacétylcholinestérase a été étudiée chez des rats. Le NMI, sel quaternaire de nicotine, qui ne traverse pas la barrière hématoencéphalique, a été administré dans de la gélatine à 6% en dosage sous-cutané de 1000 μg/ml/kg/jour pendant 14 jours. Le NMI n'a pas changé de paramètres et aucune trace de nicotine n'a été découverte dans les homogénates de cervelles complètes.

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[16] S. J. KONTUREK, J. DALE, E. D. JACOBSON and L. R. JOHNSON, Gastroenterology *62*, 425 (1972).
[17] A. ROBERT, Proc. Soc. exp. Biol. Med. *137*, 319 (1972).
[18] A. K. ARMITAGE and G. H. HALL, Nature, Lond. *214*, 977 (1967).
[19] I. Hanin and D. J. JENDEN, Biochem. Pharmac. *18*, 837 (1969).
[20] Supported in part by grants from the American Medical Association Education and Research Foundation and USPHS No. MH 17691–03. The nicotine monomethiodide was a generous gift from Professor R. B. BARLOW, Department of Pharmacology, University of Edinburgh, Edinburgh (Scotland).

Peritubular Capillary Permeability of Albumin in Saline and Water Diuresis

The significance of peritubular physical factors in the control of renal proximal tubular fluid reabsorption has received special attention in recent years. The evidence is in favor of a positive correlation between the oncotic pressure in peritubular capillaries and the rate of tubular reabsorption[1,2]. This positive correlation suggests that the oncotic pressure gradient across the peritubular capillary wall plays a significant role in the removal of tubular reabsorbate from the interstitium and in turn the tubular lumen. The extent of the gradient, however, must be dependent not only on intracapillary protein concentration but also on the concentration in the interstitium. An important factor in the regulation of interstitial protein concentration is the permeability of the peritubular capillaries. In order to provide information on this problem we have compared the mean transit time of labelled albumin from arterial blood to renal capsular and hilar lymph ($\bar{t}_{a1b}$), obtained under control conditions, with that obtained in the same kidney during saline or water diuresis. Moreover, with the aid of other tracers we have interpreted these results in terms of modulated permeability of the peritubular capillaries to albumin.

Material and methods. The experiments were carried out on chloralose anesthetized dogs. Capsular and hilar

[1] B. M. BRENNER, K. H. FALCHUCK, R. I. KEIMOWITZ and R. W. BERLINER, J. clin. Invest. *48*, 1519 (1969).
[2] E. PERSSON, B. ÅGERUP, J. SCHNERMANN, Int. Symposium on Renal Handling of Sodium. Proceedings, in press.