Effect of Arterial Oxygen Tension on Cerebral Blood Flow at Different Levels of Arterial PCO_2

Cerebral blood flow is closely correlated to carbon dioxide tension of arterial blood over a wide range of $PaCO_2$[1]. Oxygen exerts a vaso-constricting effect at high tensions, while a reduction of arterial PO_2 produces no effect until a critical level of 30–50 mm Hg is attained[2]. The effects of combined alterations in arterial oxygen and carbon dioxide tensions on cerebral blood flow, however, are largely unknown although of considerable clinical and theoretical interest. In the present study the influence of different arterial PCO_2 tensions on the cerebrovascular responsiveness to alterations of arterial PO_2 between 50–140 mm Hg was investigated.

Methods. The experiments were performed in 31 cats, anaesthetized with nembutal (30 mg/kg body weight, i.p.). After tracheotomy the animals were curarized and ventilated with a Starling pump. 15 animals (group I) were ventilated at a normal rate and normal tidal volume with N_2/O_2 mixtures of different oxygen content. PaO_2 in this group was in the range of 55–140 mm Hg; $PaCO_2$ was 28.2 $\pm$ 1.83 S.D. In 16 experiments (group II) 3–5% CO_2 was added to the above gas mixtures. $PaCO_2$ varied between 35.5 and 72.5 mm Hg (mean 47.33 $\pm$ 12.6 S.D.). PaO_2 was in the range between 50–140 mm Hg.

Arterial blood pressure (Statham pressure gauge transducers) and end-expiratory CO_2 (IR analyser) were continuously recorded. Arterial PO_2, PCO_2 and pH were determined according to the micro-method of ASTRUP. Cardiac output was measured by thermodilution technique. Blood flow through forebrain, cerebellum and brain stem was determined under steady-state conditions of PaO_2, $PaCO_2$, mean arterial blood pressure, and cardiac output by means of the particle distribution technique[3]. In group II the determination of CBF was carried out after a period of 35–40 min of 3–5% CO_2 inhalation.

Results. The results of multiple regression analysis of the data are summarized in the Table. Cerebrovascular responsiveness to changes in PaO_2 in hypercapnia differs from that observed under normocapnia. In normocapnia no correlation between PaO_2 (varying between 55–140 mm Hg) and blood flow is seen; in hypercapnia, however, a significant negative correlation between PaO_2 and blood flow through forebrain, cerebellum and brain stem is observed.

It is concluded from these data that the response to combined alterations of PaO_2 and $PaCO_2$ is not simply additive. Similar results were obtained by SHAPIRO et al.[4] in man. AGNOLI et al.[5] observed that hypoxia prevents the adaption of CBF and CSFpH to chronic hypercapnia. These authors propose that hypoxia might interfere with active transport mechanisms involved in the regulation of the extracellular pH of the central nervous system. Our findings seem to constitute another aspect of the same phenomenon, namely an increased sensitivity to hypoxia under hypercarbia.

Zusammenfassung. Die Wirkung des arteriellen O_2-Partialdruckes auf die Durchblutung des Grosshirns, Kleinhirns und Hirnstammes bei normalen und erhöhten CO_2-Partialdrucken im arteriellen Blut wird an der anaesthesierten Katze untersucht. Die Wirkung des PaO_2 ist von der Höhe des $PaCO_2$ abhängig.

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Partial correlation coefficients between PaO_2, $PaCO_2$ mean arterial blood pressure (BP) and blood flow through forebrain (CBFp), cerebellum (CBFc) and brain stem (CBFs)

	Group	$PaCO_2$	BP	CBFp	CBFc	CBFs
PaO_2	I	0.0702	0.0092	—0.4242	—0.2515	—0.1330
	II	—0.3878	0.1080	—0.7161[b]	—0.6186[a]	—0.5612[a]
$PaCO_2$	I	–	—0.0969	0.8151[c]	0.8178[c]	0.9006[c]
	II	–	0.0892	0.3661	0.5881[a]	0.1133
BP	I	–	–	—0.1860	—0.3273	—0.3105
	II	–	–	—0.0614	0.1301	0.0183

Significant correlations: [a] $0.05 > p > 0.01$. [b] $0.01 > p > 0.001$. [c] $p < 0.001$.

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Chronic Effects of Nicotine on Rat Gastric Secretion

Tobacco smoking has been implicated as a contributory factor in the aetiology, and reduced healing, of peptic ulcers[1,2]. Furthermore, nicotine has been shown to increase the ulcerogenic potential of histamine in dogs[3] and the histamine-forming capacity of the rat stomach[4]. These facts suggest that nicotine and smoking may increase gastric acid and pepsin production, however, secretory data in the literature are contradictory ([5] review). We have recently shown that acute doses of nicotine depress gastric secretion[6,7], but this may not be directly applicable to the condition resulting from chronic alkaloid exposure. Reported here are the effects of chronic nicotine

administration on basal and sub-maximal ICI-50123-induced secretion in the pylorus-ligated rat.

Materials and methods. Sixty male Sprague-Dawley rats[8] weighing 274.2 ± 4.5 g were used. They were randomly divided into 2 groups of 12 rats (controls) and 48 rats (nicotine treated) and injected s.c. 3 times daily for 15 days with either 1.0 ml/kg 0.85 g/100 g w/v sodium chloride (O.P. 262 mOs/kg water, pH 3.38, 23 °C) or 100 μg nicotine base[9]/ml/kg in sodium chloride (O.P. 267 mOs/kg water, pH 3.37, 23 °C), respectively. Details of animal care and housing, and methods of pylorus-ligation and gastric juice collection and analyses have been presented previously[10–12].

Drugs injected acutely during the 2 h of collection were as follows: ICI-50123[13] 200 μg/ml/kg/h in sodium chloride (O.P. 272 mOs/kg water, pH 9.64, 24 °C); ICI-50123 control solution, 0.85 g/100 ml w/v sodium chloride (O.P. 273 mOs/kg water, pH 10.07, 22 °C); nicotine and nicotine control solutions were similar to those used for the chronic injections. Because of the differences in pH between the nicotine and ICI-50123 injectables, rats also received injections of saline control solution at the opposite pH to that of the primary injectable to minimize any pH effect on gastric secretion[14]. Injectables were always administered at different sites using individual syringes and needles.

Results. Body weight curves are indicated in the Figure. The control and treated groups initially increased similarly by 7.8 and 7.9 g/day, respectively. Weight gain was decreased to 5.3 g/day ($P < 0.02$) after saline and to 4.2 g/day ($P < 0.001$) after nicotine; reduction in weight gain following nicotine was greater than that following saline ($P < 0.05$).

Data on gastric secretion are presented in the Table. The chronic administration of nicotine (columns A, B) doubled gastric juice volume and acid output ($P < 0.001$ and < 0.005, respectively); pepsin output was increased slightly ($P < 0.05$). The acute administration of nicotine to animals chronically exposed to nicotine (columns B, C) resulted in a halving of gastric juice volume and pepsin output ($P < 0.001$ and < 0.005), respectively); acid output was depressed 4-fold ($P < 0.001$). Sub-maximal doses of ICI-50123 in rats chronically exposed to nicotine (columns B, D) stimulated gastric juice volume slightly, but this was not significant; acid output however was about doubled ($P < 0.01$) and pepsin output depressed ($P < 0.005$). Results produced by sub-maximal doses of ICI-50123 plus acute doses of nicotine in rats chronically exposed to nicotine (columns D, E) indicated that the depression of gastric juice volume and acid and pepsin outputs seen with acute doses of nicotine alone had been abolished by the secretagogue.

Macroscopic examination of the stomach after gastric juice collection was unremarkable.

Discussion. The results presented here indicate that chronic nicotine injections of 300 μg/kg/day for 15 days result in an increased gastric juice volume, and acid and pepsin output. Based on an average 'smoking dose' of nicotine[15], this dose approximates to the smoking of 10–15 cigarettes/day. Acute nicotine administration to rats chronically exposed to the alkaloid resulted in significant secretory inhibition (which could be overcome by sub-maximal doses of ICI-50123), which is similar in magnitude to what occurs in normal rats[6,7]. It can be seen that the increase in acid output following chronic nicotine can

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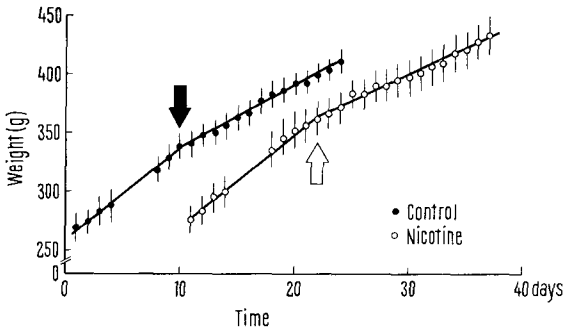
Gastric secretion in 2 h pylorus-ligated rats after chronic nicotine injections

Chronic injections	Groups: Saline	Nicotine			
Acute injections	Saline	Saline	Nicotine	ICI-50123	ICI-50123 and nicotine
	A	B	C	D	E
Gastric juice vol. (ml/2 h)	1.1 ± 0.1	2.4 ± 0.2	1.0 ± 0.2	2.8 ± 0.4	2.6 ± 0.3
Gastric juice vol. (100 g) (ml/100 g/2 h)	0.27 ± 0.02	0.59 ± 0.05	0.26 ± 0.04	0.66 ± 0.08	0.65 ± 0.07
Acid output (μEq/100 g/2 h)	17.8 ± 2.4	36.5 ± 4.6	9.3 ± 2.3	64.0 ± 10.6	47.6 ± 8.2
Pepsin output (mg/2 h)	0.51 ± 0.04	0.73 ± 0.08	0.40 ± 0.06	0.40 ± 0.05	0.72 ± 0.13
	P values				
	A:B	B:C	B:D	D:E	C:E
Gastric juice vol.	< 0.001	< 0.001	N.S.	N.S.	< 0.001
Gastric juice vol. (100 g)	< 0.001	< 0.001	N.S.	N.S.	< 0.001
Acid output	< 0.005	< 0.001	< 0.001	N.S.	< 0.001
Pepsin output	< 0.05	< 0.005	< 0.005	< 0.005	< 0.001

Data are presented as mean values ± S.E.M. for 12 rats/group. *P* values between the different treatments are indicated.

be further increased by ICI-50123; the slight fall in pepsin output may have resulted from volume changes. It is of interest that no ulcers were seen.

The reduced weight gain in control rats was probably due to the pH of the injectable. In the nicotine-treated rats the greater reduction in growth can be ascribed to the nicotine[16]. The mechanism of nicotine-induced gastric secretory stimulation with chronic exposure is not clear but may be due to enzyme induction[17,18], for example,



Body weight gain in control and nicotine-injected rats. Data are presented as mean values ± S.E.M. for 12 control (●) and 48 nicotine-injected (○) rats. The groups were run simultaneously but are separated for illustrative purposes. Day 1 for the saline (closed arrow) and nicotine injections (open arrow) are indicated. Control groups – pre-injection: r, +0.9973; $P<0.001$; Y, 299.8+7.8 (X, 5.3); post-injection: r, +0.9935; $P<0.001$; Y, 374.3+5.3 (X, 16.0). Nicotine-injected groups – pre-injection: r, +0.9954; $P<0.001$; Y, 328.2+7.9 (X, 7.3); post-injection: r, +0.9868; $P<0.001$; Y, 400.7 +4.2 (X, 19.0).

histamine[4] or other substances[19]. Results presented may explain why smoking is a contributory factor in the aetiology and healing of peptic ulcers in man[20].

Résumé. Après avoir reçu 300 µg de tartrate de nicotine-hydrogène pendant 15 jours il y eut des augmentations significatives dans le volume du suc gastrique et dans la production de pepsine. Des injections de nicotine on abaissé tous les paramètres, mais combinées avec de la gastrine synthétique (ICI-50123), elles n'ont aucun effet. Les résultats présentés peuvent expliquer pourquoi l'habitude de fumer est un facteur contribuant à la formation à la guérison des ulcères peptiques.

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Effect of Electrical Stimulation in VPM on Saccharin Preference and Water Intake in Cats[1]

Studies have shown that electrical or chemical stimulation of the tongue evokes responses in the medial part of the nucleus VPM of the thalamus[2-5]. Bilateral lesions in the same region produce an elevation of the rejection threshold for quinine solutions as well as decreases in volume intake of sucrose and sodium chloride solutions[6-8]. Studies on alimentary behavior have repeatedly pointed to the importance of taste in feeding and drinking reactions[9-15]. As a continuation of our studies on central mechanisms related to feeding behavior[16-19], we wished to gather more data concerning the role of the proposed thalamic taste relay nucleus in a preference behavioral situation[20].

Methods. The experiments were performed on 10 adult cats weighing between 3.0 and 3.6 kg. Bipolar strut electrodes were implanted bilaterally in the medial part of the VPM nucleus (A 8.5, L 3.5, H 0) in 8 cats (VPM cats) and in the region of n. lateralis posterior (A 7.5, L 5.0, H +5.5) in 2 cats (LP cats), according to the atlas by Jasper and Ajmone-Marsan[21]. Electrodes were constructed of stainless steel wires (0.2 mm in diameter) whose tips were bared.

Two weeks after surgery, the cats were water-deprived and then taken to the observation chamber. This chamber was provided with 2 feeders located on opposite sides of the cage. Each animal was trained to press the bar at the feeder and for each press 0.1 cm³ of water was automatically delivered. Every day the animal remained in the experimental cage about $^1/_2$ h until it no longer pressed the bar.

When the cat had learned to bar-press and its water intake had reached a constant level, a saccharin solution was introduced into one feeder. The animal then drank distilled water or saccharin solution according to its preference. The bottles were exchanged every few days to prevent the establishment of a habit of drinking from one feeder only. After 10 days, a control series of 20 sessions was performed on the 8 VPM animals. During these sessions the saccharin concentration was increased 0.1% daily, beginning at 0.1% and continuing until a concentration of 2% was reached. A 1-week interval followed during which the animals received water ad libitum.

In a second series of sessions, the VPM cats were divided into 2 groups. With the first group of 4 cats (CW1, CW2, CW3 and CW4), sessions similar to the above control series were repeated except that unilateral bipolar electrical stimulation was administered through the implanted electrodes. Monophasic, square-wave pulses were delivered from a Grass stimulator. The usual stimulation parameters were 0.5–1.0 V, 20 cps and 1 msec pulse duration. Each stimulation epoch consisted of 15 sec stimulation followed by a 15 sec interstimulation interval. 20 stimulation epochs were tested daily and started 30 sec after the animal was brought into the observation chamber. Following stimulation, the cat was allowed to continue to press and drink ad libitum.

The second group of 4 VPM cats was used as a 'special' control in which no stimulation was applied. After 1 week, these 4 control cats were also used for electrical stimulation studies of the VPM area. The procedure was some-