Effect of Arterial Oxygen Tension on Cerebral Blood Flow at Different Levels of Arterial PCO₂

Cerebral blood flow is closely correlated to carbon dioxide tension of arterial blood over a wide range of PaCO₂. Oxygen exerts a vaso-constricting effect at high tensions, while a reduction of arterial PO₂ produces no effect until a critical level of 30–50 mm Hg is attained. 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 PCO₂ tensions on the cerebrovascular responsiveness to alterations of arterial PO₂ 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 N₂/O₂ mixtures of different oxygen content. PaO₂ in this group was in the range of 55–140 mm Hg; PaCO₂ was 28.2 ± 1.83 S.D. In 16 experiments (group II) 3–5% CO₂ was added to the above gas mixtures. PaCO₂ varied between 35.5 and 72.5 mm Hg (mean 47.33 ± 1.62 S.D.). PaO₂ was in the range between 50–140 mm Hg.

Arterial blood pressure (Statham pressure gauge transducers) and end-expiratory CO₂ (IR analyser) were continuously recorded. Arterial PO₂, PCO₂ and pH were determined according to the micro-method of ASNRV. Cardiac output was measured by the thermodilution technique. Blood flow through forebrain, cerebellum and brain stem was determined under steady-state conditions carried out after a period of 35–40 min of 3–5% CO₂ in-nhalation. The histamine-forming capacity of the rat stomach was determined under steady-state conditions.

Results. The results of multiple regression analysis of the data are summarized in the Table. Cerebrovascular responsiveness to changes in PaO₂, PaCO₂ tensions on the cerebrovascular system. Our findings seem to constitute another aspect of the same phenomenon, namely an increased sensitivity to hypoxia under hypercarbia.

<table>
<thead>
<tr>
<th>PaO₂</th>
<th>PaCO₂</th>
<th>BP</th>
<th>CBFP</th>
<th>CBFC</th>
<th>CBFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0702</td>
<td>0.0992</td>
<td>-0.4212</td>
<td>-0.2515</td>
<td>-0.1330</td>
</tr>
<tr>
<td>2</td>
<td>-0.3878</td>
<td>0.1080</td>
<td>-0.7161</td>
<td>0.1080</td>
<td>-0.5612</td>
</tr>
<tr>
<td>3</td>
<td>0.0892</td>
<td>0.5881</td>
<td>0.1133</td>
<td></td>
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<tr>
<td>4</td>
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<td>0.9066</td>
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<td>5</td>
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<td>0.9066</td>
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<tr>
<td>6</td>
<td>-0.1860</td>
<td>0.3273</td>
<td>-0.3055</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>-0.0004</td>
<td>0.1301</td>
<td>0.0153</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significant correlations: *p < 0.05, p < 0.01, **p < 0.001.

of PaO₂, PaCO₂, mean arterial blood pressure, and cardiac output by means of the particle distribution technique. In group II the determination of CBF was carried out after a period of 35–40 min of 3–5% CO₂ in-nhalation.

It is concluded from these data that the response to combined alterations of PaO₂ and PaCO₂ is not simply additive. Similar results were obtained by Shapiro et al. in man. AGNOI et al. 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.

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. Furthermore, nicotine has been shown to increase the ulcerogenic potential of histamine in dogs and the histamine-forming capacity of the rat stomach. These facts suggest that nicotine and smoking may increase gastric acid and pepsin production, however, secretory data in the literature are contradictory. We have recently shown that acute doses of nicotine depress gastric secretion, but this may not be directly applicable to the condition resulting from chronic alkaloid exposure. Reported here are the effects of chronic nicotine exposure.
administration on basal and sub-maximal ICI-50123-induced secretion in the pylorus-ligated rat.

Materials and methods. Sixty male Sprague-Dawley rats 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/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.

Drugs injected acutely during the 2 h of collection were as follows: ICI-50123 200 μg/ml/kg 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. 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 < 0.003, respectively); acid output was depressed 4-fold (P < 0.001). Sub-maximal doses of ICI-50123 (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.

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, 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. It can be seen that the increase in acid output following chronic nicotine can be

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

<table>
<thead>
<tr>
<th>Chronic injections</th>
<th>Saline</th>
<th>Nicotine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute injections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Gastric juice vol. (ml/2 h)</td>
<td>1.1 ± 0.1</td>
<td>2.4 ± 0.2</td>
</tr>
<tr>
<td>Gastric juice vol. (100 g) (ml/100 g/2 h)</td>
<td>0.27 ± 0.02</td>
<td>0.59 ± 0.03</td>
</tr>
<tr>
<td>Acid output (μEq/100 g/2 h)</td>
<td>17.8 ± 2.4</td>
<td>36.5 ± 4.6</td>
</tr>
<tr>
<td>Pepsin output (mg/2 h)</td>
<td>0.51 ± 0.04</td>
<td>0.73 ± 0.08</td>
</tr>
</tbody>
</table>

**P values**

- A:B < 0.001
- B:C < 0.001
- B:D N.S.
- D:E N.S.
- C:E < 0.001

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

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8. Charles River Breeding Laboratories, Breeding Shed 1, North Wilmington (Mass.).