Mechanisms of some visceral effects of cigarette smoking

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Aortic chemoreceptors have been shown to be stimulated significantly by nicotine absorbed into the arterial circulation from cigarette smoke which would reflexely raise the blood pressure and pulse rate. Stimulation of carotid chemoreceptors and, possibly, J receptors in the lungs give rise to respiratory effects which are manifest as hyperpnea and augmented breaths. Stimulation of the J receptors also inhibits the patellar reflex, and may possibly be responsible for the feeling of relaxation arising out of cigarette smoking.

THE acute effects which occur upon smoking of one or two cigarettes, are an increase in the systemic blood pressure and heart rate accompanied by hyperpnea. Studies carried out on human volunteers showed[1] a significant rise in the diastolic as well as systolic blood pressure and pulse rate all of which returned to initial control levels only after about 30–60 min. Accompanying these effects, there was a drop in the alveolar end-tidal CO_2 (E_TCO_2) percentage as well, indicating hyperpnea, which also took about 30 min to return to initial control levels. These two chief visceral effects of smoking cigarettes are most likely produced by nicotine contained in the tobacco smoke and not by CO_2, CO or other irritating constituents that are also contained in it. This conclusion was arrived at in this study by giving the same volunteers cigarettes to smoke that had nicotine extracted from the tobacco; the observed effects on the cardio-respiratory system then were negligible and transitory.

In humans a third effect, a viscero-somatic reflex, also seen on smoking cigarettes, is a highly significant depression of the patellar reflex[2]. This reflex, too, seemed to be an effect of nicotine, and was absent when the same subjects were given lettuce-cigarettes (non-nicotine) to smoke.

Action of nicotine

What is the mechanism by which each effect, i.e. rise in blood pressure, augmented breaths, muscle relaxation, etc. is produced? One has to consider whether the cardio-respiratory effects are peripheral in origin or consequent to a central or spinal effect of nicotine. The first indication of a possible vagal origin of these reflexes came from animal studies by Comroe and Mortimer[3] wherein small doses of nicotine injected into the arch of the aorta of dogs, perhaps stimulated the aortic chemoreceptors to elicit the cardiovascular effects and the carotid chemoreceptors to stimulate respiration.

Mechanism of cardiovascular effects

Armitage[4] demonstrated a rise in the systemic blood pressure of cats when they were made to inhale a puff of cigarette smoke. Since this observed effect survived even after cutting of the vagi, he concluded that nicotine acted directly on the vasomotor centre to produce these responses. But in a later study[5] the pressor responses were found to be somewhat reduced after denervation of the aortic and carotid chemoreceptors, showing that a direct action of the drug on the vasomotor areas was not the main pathway for this action. Taking into consideration, evidence from Paintal and Riley[6], that aortic chemoreceptors could be stimulated by injecting nicotine into the ascending aorta, a study was undertaken in cats to see the responses of arterial chemoreceptors to the smallest doses of nicotine that could be absorbed into the arterial blood from inhaled cigarette smoke. In addition, the responses of aortic chemoreceptors were also studied when the cats were made to inhale cigarette smoke.

Methods

Cats were anaesthetized with sodium pentobarbitone. Catheters were inserted into the right femoral artery (for recording blood pressure), right saphenous vein (for subsequent doses of anaesthesia) and into the left atrium (LA) for injecting nicotine. The cats were artificially ventilated and the rectal temperature was maintained between 37 and 38°C. Single aortic chemoreceptor fibres were dissected out from the right aortic nerve and their responses to threshold doses of nicotine LA and to inhalation of small volumes of cigarette smoke (see inhalation set up, Figure 1) were recorded.

Results and discussion

All ($n \approx 51$) aortic chemoreceptors fibres that were tested were stimulated by their individual threshold doses of

nicotine, which ranged from 1 to 10 μg kg^{-1} (mean 8 μg kg^{-1}). Those fibres whose threshold dose to stimulation by nicotine LA was less than the amount of nicotine contained in a certain volume of cigarette smoke delivered were stimulated; the remaining with higher thresholds were not, showing thereby that it was nicotine and not CO_2, CO or any other constituent of smoke that was responsible for the observed stimulation. The responses of aortic chemoreceptors to both nicotine LA and inhalation of cigarette smoke were blocked after the cats were given hexamethonium (i.v.), a nicotinic receptor blocker (Figure 2). This provided unequivocal evidence that nicotine stimulated aortic chemoreceptors directly.

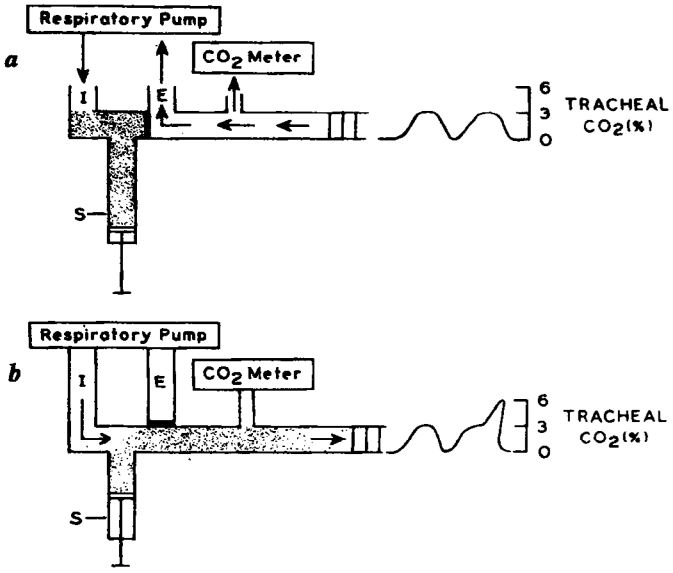

Figure 1. Schematic representation of the system used for delivering smoke. *a*, During the expiratory phase smoke is manually filled with a syringe into a side arm of the inspiratory side of the respiratory circuit. *b*, During the inspiratory phase smoke is pushed into the lungs along with air.

Significance of aortic chemoreceptor stimulation

The mean increase in the activity of aortic chemoreceptors in response to a puff of cigarette smoke was about five-fold over the resting activity, and is approximately the same as obtained by ventilating cats with fairly hypoxic gas mixtures ($PaO_2 = 40$ mm Hg). It is known[7] that hypoxia, by stimulating aortic chemoreceptors reflexely, raises systemic blood pressure and causes tachycardia. It therefore follows that stimulation of the aortic chemoreceptors by nicotine must also reflexely evoke a rise in blood pressure. Nicotine absorbed from cigarette smoke would also stimulate the carotid chemoreceptors, but it is important to note that the latter do not evoke

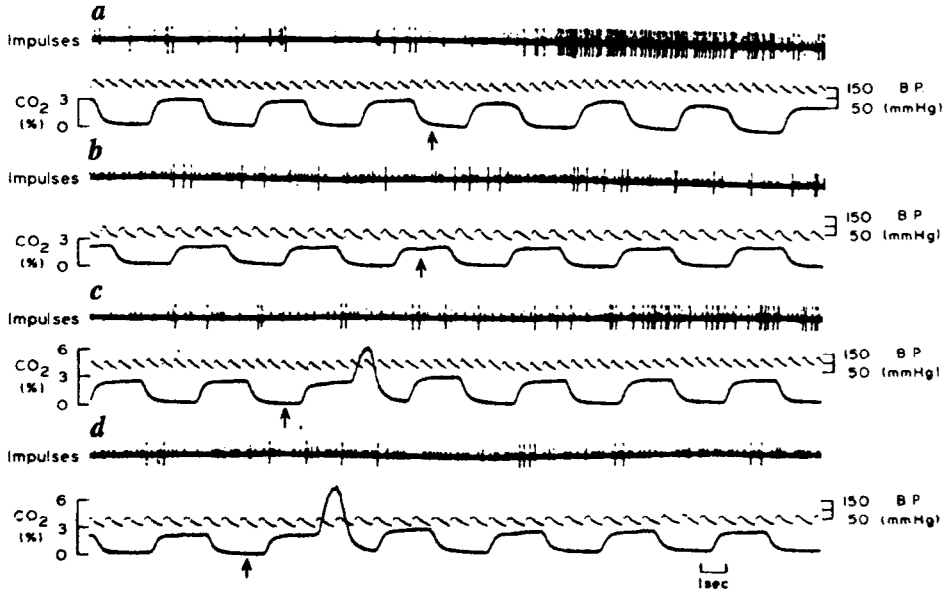

Figure 2. Records showing the responses of a single aortic chemoreceptor fibre to nicotine and cigarette smoke. *a*, Response to 5 μg kg^{-1} nicotine LA (at arrow); latency of stimulation 3.4 sec. *b*, Record after 6.4 mg kg^{-1} hexamethonium i.v., shows fibre is unresponsive to a dose higher than in *a*, i.e. 10 μg kg^{-1} (at arrow). *c*, stimulation produced by a puff of cigarette smoke delivered at arrow, the sharp rise in CO_2 signals entry of smoke into the lungs. Latency of stimulation is 9.2 sec. Note that the rise in BP is less than with 5 mg kg^{-1} nicotine LA. *d*, after hexamethonium the fibre is unresponsive to cigarette smoke. (Reproduced from Anand, A., *Resp. Physiol.*, 1996, **106**, 231–238, with kind permission from Elsevier Science – NL., Sara Burgerhart straat 25, 1055 KV Amsterdam, The Netherlands.)

pressor responses on being stimulated[3]. Thus it can be concluded that the cardiovascular responses to cigarette smoking are elicited by stimulation of aortic chemoreceptors.

Stimulation of respiration

Apart from Comroe and Mortimer's study[3] which indicated that nicotine injected into the aortic arch on reaching the carotid bodies produced a hyperpnea, there have been no corresponding studies relating to the stimulation of carotid chemoreceptors by nicotine absorbed from cigarette smoke. In cats, Zapata *et al.*[8] were able to demonstrate an increase in the entire carotid sinus nerve activity accompanied by an increased depth of inspiration in response to smoke inhalation. They found that after cutting the remaining carotid sinus nerve (one cut for recording impulses) the hyperpnea was much less than before.

In spontaneously breathing, conscious dogs augmentation of respiration could be reduced by cooling the vagi[9], indicating that the respiratory effects were produced by receptors other than chemoreceptors. Subsequently, Lee *et al.*[9] showed that these were the J or pulmonary C-fibre receptors in the lung. However a possible contribution from the vagal aortic chemoreceptors[6] in eliciting the respiratory effects has so far not been studied by these investigators[9].

Inhibition of the patellar reflex

The initial observations on humans indicated that the reduction of the patellar reflex was by nicotine of cigarette smoke[2]. Later Ginzel *et al.*[10] found that the depression of the muscle tone in lightly anaesthetized cats occurred within 1–2 sec after injecting 25 $\mu g\ kg^{-1}$ nicotine into the right atrium. According to them, such amounts seemed too small and the latency too short for the drug to have reached the spinal cord where nicotine has been shown to excite the Renshaw cells and thereby inhibit the a-motoneurones. Thus a possible mechanism of the action of nicotine could be a reflex action originating from sites reached by the drug within a few seconds after injection, possibly from the cardio-pulmonary region. This may depress the α-activity independently of any changes in the γ-system. In cats, after bilateral mid-cervical vagotomy, nicotine failed to inhibit the stretch reflex after the brief latency by which it normally occurs. It is possible that this may be a manifestation of the J-reflex on stimulation of the J receptors by nicotine. However, no clear-cut evidence emerges in this study[10] about the role of J receptors, apart from the initial effect being produced by their stimulation.

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