Regional Blood Flow in Canine Brain During Nicotine Infusion: Pentobarbital vs. Chloralose Anesthesia*

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SUMMARY

We compared vasoactive effects of intravenous nicotine (36 µg/kg/min) in regional cerebral circulations under pentobarbital and chloralose anesthesia. Experiments were conducted in three groups of dogs: Group I, pentobarbital anesthesia with fixed ventilation; Group II, chloralose anesthesia with fixed ventilation; Group III, chloralose anesthesia with free breathing. Values for regional cerebral blood flow measured with 15 µ. radioactive microspheres were used to compute regional cerebral vascular resistance (rCBR). In Group I, nicotine had no effect on rCBR in cerebral cortex, and it increased significantly rCBR in cerebellum (+17%), pons (+13%), medulla (+23%), and spinal cord (+19%). Using chloralose instead of pentobarbital in dogs with fixed ventilation (Group II), caused a significant reduction in rCBR in the cerebral cortex during nicotine, although it did not alter significantly nicotine-induced changes in rCBR in other regions of the brain. Hypocapnic alkalosis during nicotine-induced hyperventilation (Group III) resulted in significant increases in rCBR in all regions of the brain; however, the increases in rCBR in noncortical regions more than doubled those in the cerebral cortex. The present results indicate: 1) Nicotine-induced vasodilation in cerebral cortex was blunted by pentobarbital anesthesia. 2) Nicotine-induced vasodilation in cerebral cortex under chloralose anesthesia was sufficient to nullify in part the potent vasoconstrictor effect of hypocapnic alkalosis.

INTRAVERSEOUS NICOTINE activates vasomotor mechanisms which cause pronounced systemic cardiovascular responses, i.e., marked elevations in arterial blood pressure and total peripheral resistance.1-4 These mechanisms include the sympathetic ganglia (including the adrenal medulla), 5 and vasopressin released into the systemic circulation from the posterior pituitary gland.6,7 Activation of the sympatheal system is via the arterial chemoreceptors, the sympathetic ganglia (including the adenral medulla), and the central nervous system.5,8-10

We have demonstrated in pentobarbital-anesthetized, artificially-ventilated dogs that the vasomotor mechanisms activated by nicotine affect vascular resistance in cerebral cortex, but not in other regions of the brain.11 In the cerebral cortex, nicotine caused predominant beta adrenergic receptor mediated vasodilation, although it also activated alpha adrenergic (vasoconstrictor) receptors, and a non-adrenergic, non-cholinergic vasodilator mechanism.

Pentobarbital is a barbiturate which may have blunted nicotine-induced cerebral vasomotor responses in our earlier study because of its ability to 1) depress autonomic reflex pathways;12 2) depress activity and metabolic rate in the central nervous system;13 and 3) reduce responsiveness of vascular smooth muscle.14 Therefore, in the present study nicotine-induced changes in regional cerebral blood flow and vascular resistance in artificially-ventilated dogs anesthetized with pentobarbital were compared to those in artificially-ventilated dogs anesthetized with chloralose. Chloralose is a non-barbiturate general anesthetic, which is relatively free of the depressive effects of pentobarbital on cerebral vasomotor mechanisms.15,16 In addition, we assessed the strength of nicotine-induced cerebral vasodilation by testing its ability to override the cerebral vasoconstrictor effect of chemoreflex-mediated hypocapnic alkalosis in chloralose-anesthetized, free-breathing dogs.

Methods

Experiments were performed in 21 mongrel dogs of both sexes ranging in weight from 16 to 24 kg. These dogs were randomly divided into three equal groups. Dogs of Group I were anesthetized with pentobarbital sodium, 30 mg/kg i.v., while dogs of Groups II and III were anesthetized with alpha chloralose, 100 mg/kg.
Table 1

**Effect of Nicotine on Systemic Hemodynamic Parameters in Dogs Anesthetized with Pentobarbital under Fixed Ventilation and in Dogs Anesthetized with Chloralose under Fixed Ventilation and Free Breathing**

<table>
<thead>
<tr>
<th></th>
<th>Pentobarbital (Fixed ventilation (n = 7))</th>
<th>Chloralose (Fixed ventilation (n = 7))</th>
<th>Chloralose (Free breathing (n = 7))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Nicotine</td>
<td>Control</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>138 ± 4</td>
<td>200 ± 10*</td>
<td>127 ± 6</td>
</tr>
<tr>
<td>Mean central venous pressure (mm Hg)</td>
<td>7 ± 2</td>
<td>10 ± 2*</td>
<td>3 ± 0.6</td>
</tr>
<tr>
<td>Heart rate (beats/mm)</td>
<td>156 ± 9</td>
<td>150 ± 17</td>
<td>142 ± 14</td>
</tr>
</tbody>
</table>

*p < 0.05, effect of nicotine. Values are mean ± SE.
for regional cerebral vascular resistance (rCVR). Nicotine infusion in the dogs of Group I had no significant effect on rCVR in cerebral cortex, but it increased rCVR in cerebellum (+17%), pons (+13%), medulla (+23%), and spinal cord (+19%) (fig. 1).

Group II. Effects of Nicotine in Chloralose-Anesthetized, Artificially-Ventilated Dogs. Nicotine-induced changes in systemic hemodynamic parameters (table 1) and arterial blood gases (table 2) in chloralose-anesthetized, artificially-ventilated dogs of Group II were directionally similar to those in the pentobarbital-anesthetized, artificially-ventilated dogs of Group I. However, increases in mean aortic blood pressure (+97%) and mean central venous pressure (+167%) were significantly greater in the chloralose group. Nicotine-induced increases in rCBF in these artificially-ventilated dogs anesthetized with chloralose (cerebral cortex, +348%; cerebellum, +169%; pons, +81%; medulla, +40%; spinal cord, +55%) (table 2) were greater than those in the artificially-ventilated dogs anesthetized with pentobarbital (Group I). In dogs of Group II nicotine reduced significantly rCVR in cerebral cortex, it tended to reduce rCVR in cerebellum, and it increased rCVR in other regions of the brain (fig. 1).

Group III. Effect of Nicotine in Chloralose-Anesthetized, Free-Breathing Dogs. In chloralose-anesthetized, free-breathing dogs, nicotine increased mean aortic pressure (+64%), and mean central venous pressure (+150%), and it caused no significant change in heart rate (table 1). Under these free-breathing conditions, nicotine-induced hyperventilation was associated with a significant decrease in arterial PCO₂ and a significant increase in arterial pH, although arterial PO₂ remained normal (table 2). In spite of significant hypertension in the dogs of Group III, nicotine had no effect on rCBF in cerebral cortex, it caused significant, approximately 30%, reductions in rCBF in other regions of brain (table 2).

In free-breathing, chloralose-anesthetized dogs, hyperventilation during nicotine caused an increase in rCVR all regions of the brain (fig. 1). However, the nicotine-induced increases in rCVR in non-cortical regions were more than double those in the cerebral cortex.

Discussion

We used the microsphere method to measure regional cerebral blood flow. This method has particular value in brain because of its structural and functional heterogeneity. Furthermore, the complex anatomical arrangement of the cerebral circulation renders more direct methods of flow measurement, e.g., electromagnetic flowmeter, inapplicable. Fifteen micron radioactive microspheres were chosen because microspheres of this size had been reported to demonstrate 1) essentially complete entrapment in the cerebral microvasculature, 2) no artifactual distortion of regional cerebral blood flow distributions, and 3) reproducible measurements of both total and regional cerebral blood flow. 19
The major findings of this study were: 1) Nicotine infusion caused vasodilation in the cerebral cortex of artificially-ventilated dogs anesthetized with chloralose, but it had no vasomotor effect in the cerebral cortex of artificially-ventilated dogs anesthetized with pentobarbital. 2) Under chloralose anesthesia, nicotine-induced cortical vasodilation blunted severely the vasoconstrictor effects of hypocapnic alkalosis which occurred when chemoreflex hyperventilation was permitted during nicotine infusion.

The present results confirm those of our previous investigation indicating that nicotine infusion in pentobarbital-anesthetized, artificially-ventilated dogs caused pronounced aortic hypertension, which was accompanied by no change in vascular resistance in the cerebral cortex and by an increase in vascular resistance in other regions of the brain. In our previous investigation, we conducted additional studies to define the vasomotor mechanisms underlying these effects of nicotine in the regional cerebral circulations. These studies were conducted with aortic pressure held constant to preclude cerebral vasoconstriction due to pressure-flow autoregulation. Our results indicated that nicotine activated several vasomotor mechanisms in the cerebral cortex, although it had no vasomotor effects in non-cortical regions. This regional variation was consistent with greater concentrations of adrenergic receptors and sympathetic nerve fibers in the cerebral cortex. Under constant pressure conditions, nicotine caused an increase in blood flow in the cerebral cortex, which was prevented with propranolol. Thus, nicotine activated a cortical vasodilator mechanism mediated via the beta adrenergic receptors. However, our further finding that nicotine caused again an increase in cortical flow when phenoxybenzamine was administered along with propranolol indicated that nicotine also activated an alpha adrenergic vasoconstrictor mechanism, as well as a non-adrenergic vasodilator mechanism. Since we found that this non-adrenergic vasodilator mechanism activated by nicotine persisted after atropine administration, it was not mediated via cerebral cholinergic receptors. Possible mechanisms for this non-adrenergic, non-cholinergic vasodilation in cerebral cortex during nicotine infusion were direct relaxation of cerebral vascular smooth muscle, and/or metabolically-induced vasodilation secondary to arousal of the central nervous system.

The present findings demonstrate a pronounced reduction in cortical vascular resistance during nicotine in artificially-ventilated dogs when chloralose was used, but no change in cortical vascular resistance during nicotine when pentobarbital was used. Thus, under chloralose anesthesia, but not under pentobarbital anesthesia, nicotine-induced vasodilator mechanisms were sufficient to cause cortical vasodilation in spite of competition from concurrently activated vasoconstrictor mechanisms, i.e., pressure-flow autoregulation and alpha adrenergic receptor-mediated vasoconstriction. This suggests that pentobarbital anesthesia inhibited mechanism(s) of cortical vasodilation during nicotine infusion.

There are several possible cortical vasodilator mechanisms which may have been inhibited by pentobarbital anesthesia. Because of the demonstrated ability of pentobarbital anesthesia to depress chemoreflex mechanisms, autonomic ganglia, and the central nervous system, pentobarbital may have blunted nicotine-induced release of norepinephrine from central sympathetic nerve terminals. Although norepinephrine causes vasoconstriction in most vascular beds, its local effect in the cerebral circulation is vasodilation, because of the unusually low sensitivity of alpha receptors there. Also, it is possible that pentobarbital impaired non-adrenergic, non-cholinergic vasodilation in cerebral cortex because of its ability to decrease cerebral metabolic rate. Finally, pentobarbital attenuated the increase in intravascular pressure during nicotine, which reduced the stimulus for physical distension of cortical vessels.

Nicotine caused the same vasomotor changes in non-cortical regions in chloralose-anesthetized dogs as it did in pentobarbital-anesthetized dogs. This result indicates that the lack of direct effect of nicotine in non-cortical regions in our previous study was due to an inherent insensitivity of these regions to the vasomotor mechanisms activated by nicotine and not due to depression of these mechanisms by pentobarbital anesthesia.

When chloralose-anesthetized dogs breathed freely, hyperventilation was observed during nicotine infusion, which resulted in marked reductions in PCO2 and elevations in pH. This hyperventilation response is mediated via the arterial chemoreceptors. Since hypocapnic alkalosis is a potent cerebral vasoconstrictor, responses in free-breathing dogs provided a gauge of the strength of nicotine-induced cortical vasodilation. Hypocapnic alkalosis alone has been observed to cause essentially uniform increases in regional cerebral vascular resistance in chloralose-anesthetized dogs. However, our data indicate that hyperventilation during nicotine increased to a significantly lesser extent vascular resistance in cerebral cortex compared to other regions of brain. These results are consistent with our finding of selective nicotine-induced vasodilation in the cerebral cortex in chloralose-anesthetized dogs whose ventilation was held constant. They also indicate that the cortical vasodilator mechanism activated by nicotine was sufficiently potent to nullify a significant portion of the vasoconstrictor effect of hypocapnic alkalosis.

Nicotine-induced increases in aortic pressure in artificially-ventilated dogs were greater under chloralose anesthesia than under pentobarbital anesthesia. This is consistent with lesser depression of cardiovascular reflex pathways by chloralose than by pentobarbital.

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References

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