Title: MODULATING ROLE OF DOPAMINE ON ANESTHETIC REQUIREMENTS

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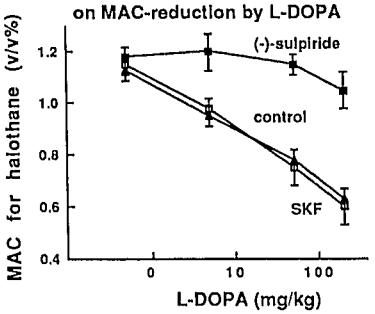
Introduction: Endogenous and exogenous dopamine may be important determinants of anesthetic requirements. Administration of the dopamine agonist, apomorphine, increases pain threshold in rats in a dose-dependent manner.[1] Levodopa (L-DOPA) administration decreased the halothane MAC in dogs although the mechanism for this change in anesthetic requirement is not known.[2] In this investigation central nervous system dopamine was increased by exogenous levodopa (L-DOPA) and decreased by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP selectively destroys dopaminergic neurons of the substantia nigra in man and mice and induces a syndrome which has virtually all the functional and neurochemical features of idiopathic Parkinson's disease.[3] We have studied: 1) the mechanism for the MAC-reducing effect of dopamine; 2) the anesthetic requirements in an animal model of Parkinson's disease; and 3) whether anesthetic requirements are normalized in this animal model following repletion of dopamine with exogenous L-DOPA.

Methods: This study was approved by our institutional Animal Care and Use Committee. Male C57BL/6IMR mice (9-12 months) were used in all the studies. L-DOPA, 5, 50 and 200 mg/kg, or its vehicle, was administered i.p. with carbidopa (CD) 25 mg/kg, a peripheral amino acid decarboxylase inhibitor, to prevent enzymatic conversion of L-DOPA to dopamine in peripheral tissue. MAC for halothane was then determined.[4] The peripheral dopamine agonist dopexamine, 0.25, 2.5 and 10 mg/kg or its vehicle, ascorbate, was administered 30 min prior to determination of MAC to examine whether changes in MAC were mediated by central or peripheral dopamine receptors. The D_1 dopamine antagonist, SKF-83566, and D_2 dopamine antagonist, (-)-sulpiride, were used to characterize the receptor subtype that mediated the L-DOPA changes in MAC. L-DOPA + CD were administered as described above and 45 min prior to determination of MAC, the dopamine antagonists were administered. MPTP, 20 mg/kg or its vehicle, 0.9% saline, were administered i.p. and 7 d later MAC was determined. In separate experiments L-DOPA, 200 mg/kg + CD were administered to characterize the effects of repletion of striatal dopamine on MAC in MPTP-treated animals. Striatal dopamine was determined by electrochemical detection i) in control mice, ii) following L-DOPA, 200 mg/kg, + CD administration, iii) 7 days after MPTP treatment, and iv) following L-DOPA + CD administration in MPTP-treated mice. Analysis of variance (ANOVA) followed by Student's unpaired t-test with Bonferroni correction, were applied to evaluate the significance of the results. Each experiment was performed in duplicate using 12 mice for each treatment dose.

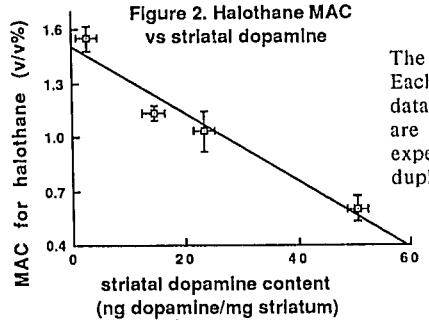
Results: L-DOPA dose-dependently decreased halothane MAC ($p<0.05$) (Figure 1) while dopexamine, the peripheral dopamine agonist, was without effect. Administration of (-)-sulpiride (D_2 antagonist) blocked the MAC-reducing action of L-DOPA, while SKF-83566 (D_1 antagonist) had no effect (Figure 1). MPTP increased the MAC for halothane by 37% ($p<0.05$) and decreased striatal dopamine by 82% ($p<0.05$). In MPTP-treated mice, repletion of dopamine with L-DOPA, 200 mg/kg, restored the MAC for halothane back to the control state. There was a highly significant negative correlation ($r^2=0.95$) between striatal dopamine and halothane anesthetic requirements (Figure 2).

Figure 1. Effect of antagonists on MAC-reduction by L-DOPA



At each dose a total of 12 mice were tested. Data are the mean and SD of experiments performed in duplicate.

Figure 2. Halothane MAC vs striatal dopamine



The r^2 value is 0.95. Each point represents data from 12 mice. Data are the mean and SD of experiments performed in duplicate.

Discussion: These data suggest that: 1) central D_2 dopamine receptors mediate the reduction of anesthetic requirements caused by L-DOPA, and that 2) striatal dopamine content is an important determinant of anesthetic requirements.

Although the usual cautions should apply when extrapolating conclusions from an experimental to a clinical setting, we speculate that in the acute situation, anesthetic requirements in patients with Parkinson's disease will be altered by loss of substantia nigra neurons and L-DOPA treatment. Thus, careful titration of the anesthetic dose may be required to prevent under- or over-dosing with anesthetic agents in patients with Parkinson's disease.

Nicoll has suggested that general anesthesia produced by volatile agents is characterized electrophysiologically by membrane hyperpolarization through an increase in membrane potassium conductance.[5] Dopamine acting on D_2 receptors in the rat substantia nigra also caused membrane hyperpolarization by an increase in membrane potassium conductance.[6] Thus, it is possible that dopamine agonists supplement the anesthetized state by membrane hyperpolarization, as a result of an increase in membrane potassium conductance mediated by D_2 receptors in the central nervous system.

References:

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