

Effect of sabcomeline on muscarinic and dopamine receptor binding in intact mouse brain

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Sabcomeline [(*R*-(*Z*)-(+)- α -(methoxyamino)-1-azabicyclo[2.2.2]octane-3-acetonitrile)] is a potent and functionally selective muscarinic M₁ receptor partial agonist. However, little is known of the binding properties of sabcomeline under *in vivo* conditions. In this study, muscarinic receptor occupancy by sabcomeline in mouse brain regions and heart was estimated using [³H]quinuclidinyl benzilate (QNB) and [³H]*N*-methylpiperidyl benzilate (NMPB) as radioligands. In the cerebral cortex, hippocampus, and striatum, the estimated IC₅₀ value of sabcomeline for [³H]NMPB binding was almost 0.2 mg/kg. Sabcomeline was not a selective ligand to M₁ receptors as compared with biperiden *in vivo*. In the cerebral cortex, maximum receptor occupancy was observed about 1 hr after intravenous injection of sabcomeline (0.3 mg/kg), and the binding availability of mACh receptors had almost returned to the control level by 3–4 hr. These findings indicated that the binding kinetics of sabcomeline is rather rapid in mouse brain. Examination of dopamine D₂ receptor binding revealed that sabcomeline affected the kinetics of both [³H]raclopride and [³H]*N*-methylspiperone (NMSP) binding in the striatum. It significantly decreased the k_3 and k_4 of [³H]raclopride binding resulting in an increase in binding potential ($BP = k_3/k_4 = B_{max}/K_d$) in sabcomeline-treated mice, and an approximately 15% decrease in k_3 of [³H]NMSP binding was also observed. Although the mechanism is still unclear, sabcomeline altered dopamine D₂ receptor affinity or availability by modulations via neural networks.

Key words: sabcomeline, mice, *in vivo*, muscarinic acetylcholine receptor, dopamine D₂ receptor