Dopamine–Acetylcholine Interactions in the Modulation of Glutamate Release

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Schizophrenia is a neurological disease whose precise anatomic substrate and cellular mechanisms are largely unknown. Internally generated voices and auditory hallucinations are among the recurrent symptoms characteristic of schizophrenia, suggestive of an impaired function of the temporal lobes.[1,2] Several neurotransmitters appear to be involved in the pathophysiology of schizophrenia, including dopamine,[3] acetylcholine,[4] and glutamate.[5] The "dopamine hypothesis," supported by pharmacological and clinical studies, proposes that an excess of dopamine or dopamine sensitivity might be associated with the disease.[3] Acetylcholine, secreted by a complex of nuclei in the basal forebrain, is an important regulator of cerebral functions such as learning and memory, sleep and wake cycles, and attention.[6] Among its cellular effects, acetylcholine binds to muscarinic receptors depressing the release of glutamate, the main excitatory neurotransmitter in the brain. Muscarinic reduction of glutamate release has been observed in many brain areas including the amygdala,[7] the hypothalamus,[8] basal ganglia,[9] and visual cortex.[10] These data suggest that the reduction of glutamate release is a general mechanism for limiting other potent excitatory effects of acetylcholine such as blockage of K^+ channels[11] and potentiation of NMDAR-mediated currents.[12] Both dopamine and acetylcholine act on complex cascades involving multiple intracellular pathways potentially interacting with each other. We considered the possibility that dopamine affects the capability of acetylcholine to depress glutamate release in the temporal cortex. Using patch-clamp recording in a thin slice preparation, we measured pharmacologically isolated AMPAR-mediated currents from visually identified pyramidal cells of layer II/III. We evoked monosynaptic glutamatergic currents (EPSCs) stimulating the neighboring axons with two current pulses at 50 ms, delivered every 6 seconds.

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Dopamine and the muscarinic agonist oxotremorine were used at 20 μM and 10 μM, respectively.

We first separately determined the direct effect of dopamine and oxotremorine on the glutamatergic currents. Consistent with previous results, oxotremorine depressed the amplitude of EPSCs (A) and increased pair pulse facilitation (PPF) both in the prefrontal cortex ($A_{oxo}/A_{ctrl} = 0.37 \pm 0.16$, $PPF_{oxo}/PPF_{ctrl} = 1.55 \pm 0.21$), taken as control, and in the temporal cortex ($A_{oxo}/A_{ctrl} = 0.48 \pm 0.04$, $PPF_{oxo}/PPF_{ctrl} = 1.53 \pm 0.31$). On the contrary, dopamine had different effects in the two brain areas, since it depressed glutamatergic currents in the prefrontal cortex ($A_{DA}/A_{ctrl} = 0.55 \pm 0.09$) but left the signal unchanged in the temporal cortex ($A_{DA}/A_{ctrl} = 1.12 \pm 0.14$). In order to test possible interactions between the two neurotransmitters in the temporal cortex, we tested the effect of acetylcholine in the presence of dopamine. In the presence of dopamine, acetylcholine failed to reduce the amplitude of the glutamatergic synaptic current ($A_{DA+oxo}/A_{ctrl} = 0.87 \pm 0.05$), as well as to change pair pulse facilitation ($PPF_{oxo}/PPF_{ctrl} = 1.0 \pm 0.11$). Inverting the order of application (oxotremorine preceding dopamine) resulted in the expected depression of the glutamatergic signal ($A_{oxo}/A_{DA} = 0.69 \pm 0.12$) but was not followed by a recovery of the glutamatergic signal ($A_{oxo}+DA/A_{ctrl} = 0.67 \pm 0.12$). Our results confirm that acetylcholine depresses glutamatergic signals, probably acting through presynaptic receptors, and suggest that dopamine has distinct effects on the release of glutamate in different brain areas. More importantly, they indicate that the presence of dopamine in the temporal cortex prevents acetylcholine from depressing the glutamatergic signals, presumably via a presynaptic interaction with muscarinic receptors. The failure of dopamine to revert the muscarinic-induced depression of glutamate release once it began suggests that dopamine acts upstream or at an intermediate level in the muscarinic second-messenger cascade.

We speculate that an increase in the release of dopamine due to an altered interaction between the frontal cortex and dopaminergic nuclei can compromise the physiologic reduction of glutamatergic currents following activation of the cholinergic nuclei. An enduring impairment of the cholinergic reduction of glutamate release might result in multiple long-term consequences, such as glutamate-induced toxicity, under- or overexpression of glutamate and monoamine transporters, and redistribution of glutamate receptors. These alterations could compromise the function of the neuronal circuitry leading eventually to a temporal cortex component in schizophrenia.

Further investigation is required to establish the biochemical nature of the muscarinic–dopaminic interaction as well as the clinical implications of our finding.

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