RESEARCH HIGHLIGHT

A new specific neuronal modulatory effect of nicotine: the functional cross talk between nicotinic and glutamate receptors

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We here have addressed the topic of the cross-talk between receptors. We provide evidence supporting the co-localization and the functional interaction between nicotinic acetylcholine receptors and some glutamatergic receptors. The recruitment of nicotinic acetylcholine receptors dynamically and negatively modulates the function of both N-methyl-D-aspartic acid (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors throughout their selective internalization. The nicotinic control of NMDA and α-AMPA receptors is operative even at very low concentrations of nicotine. Nicotinic and glutamatergic receptors have been both implicated in important pathologies such as Alzheimer's and Parkinson's disease and schizophrenia. Thus, a more extensive and detailed knowledge of this new modulatory role of nicotine may eventually enable us to develop specific therapeutic interventions for these pathologies.

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The nicotinic acetylcholine receptors (nAChRs) are fast ionotropic receptor channels present and widely distributed throughout the central nervous system (CNS) of mammals. This class includes several receptor subtypes with different pharmacological and physiologi-cal features which mainly depend on their subunits composition [1,2]. In the CNS, these receptors subtypes are expressed and functionally operating mostly at the membrane level in neurons or glial cells, where -when activated- they modulate the release of many neurotransmitters [3,4]. Their stimulatory effect, which is in turn linked to the permeability to cations [5], may be different according to the specific receptor subtypes involved [6-9]. Beside the releasing effect, the opening of nAChR channels can also trigger other functional events including activation of second messenger pathways and induction of gene transcription [10,11]. Depending on the ion flux subsequent to the activation of nAChRs modifications of the receptor cytoplasmic domain(s) may take place because of the activation of cytosolic phosphorylative processes or following changes in the redox state. These adaptations can give rise to differences in functional responsiveness of the neuron not only to nicotine, but even to other neurotransmitters. Therefore, at the nerve terminal level,

nicotine may not only induce neurotransmitter release but, throughout the interaction with other co-existing receptors, it may also exert functional modulatory role on central neurotransmission as well as on the functions of colocalized receptors [4,12-15]. In this regard, the interactions occurring between nAChRs and glutamate receptors, considering the role of glutamate in several aspects of nicotine dependence [16], neuronal plasticity as well as in the processes of learning and memory [17].

In a recent study of our group entitled "Prolonged nicotine exposure down-regulates presynaptic N-methyl-D-aspartic acid (NMDA) receptors in dopaminergic terminals of the rat nucleus accumbens" [18], we have addressed the topic of the cross-talk between receptors, and particularly between nAChRs and the glutamate receptors present on the same neuron. We provided immunocytochemical and neurochemical evidences supporting the co-localization and the functional interaction between nAChRs and NMDA receptors in dopaminergic terminals of the rat nucleus accumbens. We showed that brief pretreatment in vitro with nicotine for few minutes decreased the NMDA-induced dopamine release from nucleus accumbens nerve terminals, indicating that the recruitment of nAChRs dynamically and negatively regulates NMDA receptors through the selective internalization of GluN2B-NMDA receptors.

Inasmuch, in a previous paper, our group had also demonstrated that nicotine caused a decrease of the amount of neuronal α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors present in the same dopaminergic nerve terminals [19]. This effect was found to be selective for AMPA receptors on noradrenergic nerve endings [20], and did not occur to AMPA receptors present on gamma-aminobutyric acid (GABA) and cholinergic nerve terminals [21]. Likewise, the modulatory action of nicotine has been associated to the internalization of the GluA2 subunit of the AMPA receptors. Interestingly, the nAChR involved in dopamine release in the nucleus accumbens belongs to several nAChR subtypes (likely α6β3β2, α6α4β3β2, α4β2 and/or α4α5β2) [22] but not to the α7 nAChR subtype. These studies have been extended to explore whether the nicotine-glutamate receptors cross-talk concerns also the modulation of other neurotransmitters such as glutamate and GABA, whose release is also stimulated by α7 nAChR subtypes [9,23] and by glutamatergic NMDA and AMPA receptors [21,24]. The results are very striking and show that this modulatory action seems to be selective and involve some receptor systems and not others (unpublished observations).

These events can be summarized with the term "metamodulation" (as proposed by Katz and Edwards in the late 1990) [25]. Metamodulation refers to the possibility that different neurotransmitters can cooperate to modulate neurotransmission in the CNS. Actually, although neurotransmitters are often analyzed individually for their mediated effects, it is largely recognized that they can cooperate to reciprocally interact in controlling neuronal activity. The complexity that originates from that converging action is impressive and might account for the modulation of synaptic plasticity in selected CNS regions. For instance, the pharmacological effect exerted by nicotine described here reduces glutamate-induced release of dopamine by favoring NMDA or AMPA receptor internalization. This effect could be classified as "disenabling" and it could take place because of the co-existence of two classes of presynaptic heteroreceptors (namely the nicotinic and the glutamatergic ionotropic receptors) on the same terminals. Because of these disenabling interactions, nicotine acting at presynaptic nicotinic heteroreceptors reduces the effectiveness of another neurotransmitter (i.e. glutamate), converging its action on common target terminals (i.e. the dopaminergic terminals).

This nicotinic control of DA release through the modulation of NMDA and AMPA receptor-mediated functions may represent an important neuronal adaptation associated with nicotine assumption [19]. Notably, it appears to occur independently upon the nicotinic stimulation of the release of neurotransmitters and, what is really significant, is operative even at low concentrations of nicotine. It can be therefore well correlated with plasma and neuronal levels of nicotine compatible with those found in smokers or possibly in patients receiving a nicotine replacement therapy [26]. In addition this functional cross-talk appears quite selective according to the glutamatergic or nAChR subtypes involved (unpublished observations) .

Both nicotinic and glutamatergic receptors have been implicated in important neurological and psychiatric disorders. Moreover, they are also involved in cognitive functions and, of course, in the processes of nicotine dependence [27,28]. However, there is still much to investigate on the consequences of changes in the cholinergic and glutamatergic systems and how they may affect the functioning of the brain. It is therefore not easy to foresee whether these nicotine-induced modulatory effects of the glutamatergic receptor function might have a role in the above mentioned pathologies. Thus, it is possible that this nicotine-induced neuro-adaptation of a

specific glutamatergic receptor subtype could represent a drug-induced impairment in the glutamatergic control of dopamine release, which may in turn play a role in the mechanism of nicotine addiction. Furthermore, these mechanisms of adaptation should also be relevant to understand the interplay between nAChR and NMDAR/AMPAR in the processes of neuronal plasticity as well as in the mechanisms of learning and memory [17,]. Thus, a more extensive and detailed neurochemical and functional knowledge of this new modulatory role of nicotine may eventually enable us to develop and optimize original specific therapeutic interventions.

Conflicting interests

The authors have declared that no competing interests exist.

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