A.1 - NEURONAL NICOTINIC RECEPTORS

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Neuronal nicotinic receptors

Ionotropic neuronal nicotinic acetylcholine receptors (nAChRs) are a heterogeneous class of cationic channels widely distributed in the nervous system whose opening is controlled by the endogenous neurotransmitter acetylcholine (ACh). They consist of five subunits, and their different subunit compositions generates distinct receptor subtypes with particular functional responses to ACh and drugs. nAChR activation excites target cells, and may mediate fast synaptic transmission (e.g. in autonomous ganglionic neurons and restricted brain areas) or modulate the release of almost all neurotransmitters. nAChRs are involved in a wide range of physiological functions in the central and peripheral nervous systems, and changes in their number and/or function are associated with a number of pathophysiological conditions. They are also the targets of nicotine (the most common drug of abuse), whose complex activities in the nervous system are due to its ability to mimic the activity of ACh on this receptor subset. The different effects of nicotinic drugs is determined by the functional features and location of the nAChR subtypes with which they interact in specific neuronal systems.

We are interested in identifying and characterising the nAChR subtypes expressed in different areas of the CNS, and studying their involvement in physiological functions and in various pathological conditions, including Alzheimer's and Parkinson's diseases, some forms of epilepsy, depression, autism and schizophrenia.

Subunit composition, stoichiometry and trafficking of native subtypes

nAChRs, a very heterogeneous family of subtypes formed by the pentameric assembly of identical (homomeric receptors) or homologous subunits (heteromeric receptors) around a central ion pore, have different structural, functional, and pharmacological properties. Two main classes have been identified: alphaBungarotoxin (alphaBgtx)-sensitive receptors, which are made up of the alpha7, alpha8, alpha9 and/or alpha10 subunits and can form homomeric or heteromeric receptors, and alphaBgtx-insensitive receptors, which are heteromeric receptors that consist of alpha2-alpha6 and beta2-beta4 subunits, and bind nicotine with high affinity and many other nicotinic agonists but not alphaBgtx (Gotti et al., 2006).

The identification of the different native nAChR subtypes and their specific roles was initially hampered by the lack of subtype–specific ligands, and the fact that many neuronal cells express multiple subtypes. However the recent availability of genetically engineered knockout (Ko) or knockin (Kin) mice has made it possible to analyse the pharmacology and functional role of nAChRs in complex neurobiological systems, and to correlate major phenotypes with individual nAChR subtypes.

Our group has established the subunit composition of nAChR subtypes in different areas of the CNS of several vertebrate species using subunit-specific antibodies, immunoprecipitation and immunopurification techniques and tissues from wild type, Ko and lesioned animals (reviewed in Gotti et al., 2006). Fig. 1 shows the subtypes identified in rodent CNS by us and others.

We have recently biochemically characterised the native subtypes present in the interpeduncular nucleus and medial habenula, two areas that express the mRNA for many nAChR subunits. Moreover, we have also shown that only the alpha3beta4* and alpha3beta3beta4 subtypes mediate the release of ACh from interpeduncular nucleus synaptosomes (Grady et al., 2009).

In addition to the differences in their subunit composition, nAChR subtypes may have different subunit stoichiometries even with the same subunit composition. Electrophysiological and biochemical studies of heterologously expressed alpha4beta2 subtype have shown that differences in alpha4beta2 subunit stoichiometry can lead to subtypes with different pharmacological and functional properties.
Using functional and biochemical techniques, we have recently shown that cortical and thalamic nAChRs in heterozygous α4β2 and β2α4 mice have different relative expressions of α4 and β2 subunits, and that this correlates with differences in the functional properties of native nAChRs (Gotti et al 2008). Overall, these findings support the conclusion that α4β2 nAChRs with different stoichiometries are expressed in native tissues.

**SELECTED PUBLICATIONS**


**nAChR and neurotransmitter receptor regulation by long-term exposure to nicotine and nicotinic drugs**

Studies of the brains of tobacco smokers and animals have shown that long-term exposure to nicotine often triggers an increase in the number of nAChRs (up-regulation). This particular effect may be due to the fact that nicotine acts as both agonist and a time-averaged antagonist.

We and others have shown that the most up-regulated receptor is the alpha4beta2 subtype, but there is considerable disagreement concerning the in vivo regulation of the number and function of the other native subtypes. We are studying whether different methods of nicotine administration lead to different brain nicotine levels and/or kinetics that can differently affect the number and function of the different nAChR subtypes. This will open up possible new strategies for controlling smoking behaviours.

Over the last few years, various studies of different brain areas have shown that the effects of nicotine on synaptic connections within neuronal networks can outlast nAChR stimulation and sensitisation and alter the properties of the neuronal network by modulating excitatory and inhibitory neurons. This can lead to changes in overall network activity, that ultimately determine the altered cognitive performance observed with nicotine.

We are studying whether chronic treatment with nicotine and other nicotinic compounds not only modulate nAChR subtypes but also the number, subunit composition or location of other neurotransmitter receptors in the different brain areas, such as ionotropic and metabotropic glutamate receptors and G protein coupled D1, D2 and D3 dopamine receptors.

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