D.1 – NEURONAL NICOTINIC RECEPTORS AS TARGETS IN PATHOLOGY

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Neuronal nicotinic acetylcholine receptors (nAChRs) are ubiquitous signalling molecules and therefore involved in a wide variety of diseases affecting neuronal and non-neuronal tissues. Our research concentrates on two aspects: the role of nAChRs in degenerative brain diseases such as Alzheimer’s disease (AD) and Parkinson’s disease (PD), and their role in diseases characterised by particular mutations in the genes encoding the subunits of nAChRs. As we believe that a pharmacological approach to these pathologies could be useful therapeutically, we also synthesise and investigate novel nAChR-specific drugs.

nAChRs in AD and PD

It is thought that nicotinic transmission participates in many cognitive processes. Furthermore, lesions of the forebrain cholinergic system lead to cognitive deficits that can be reversed by nicotine. These findings, together with the fact that brain cholinergic function is impaired in patients with AD and epidemiological studies have demonstrated a significantly reduced incidence of AD and PD in smokers, have contributed to the formulation of a cholinergic hypothesis to explain the cognitive defects associated with these neurodegenerative disorders (reviewed in Gotti and Clementi, 2004).

Experimental rodent and monkey models of PD (Quik et al. 2005), and studies of human patients (Gotti et al. 2006) have shown that there is a selective decrease in the number of alpha6- alpha4- and beta2-containing receptors in the striatum and a decrease in the number of alpha4-containing receptors in the cerebral cortex (see Fig. 1; Gotti et al, 2006).

Future studies will consider the effects of smoking and other chronic drug treatments on nAChR subtype composition and distribution in the human brain areas associated with nicotine addiction.

Figure 1
Nicotinic receptor binding (left) and immunoprecipitation (right) measured in the temporal cortex (top) and caudate-putamen specimens (bottom) taken from control, PD, AD and DLB human patients.

nAChRs and ADNFLE

Recent advances in genetic analysis have led to the identification of particular mutations in the genes encoding the subunits of nAChRs that are associated with a form of sleep-related epilepsy called autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) with familial occurrence. We have recently created an inducible mouse model of ADNFLE carrying the V287L mutation of the beta2 subunit of nAChR, and found that silencing the transgene expression during brain development is sufficient to prevent the occurrence of the epileptic seizures observed in untreated adult mutant mice. This indicates that beta2* mutant receptors play a major role in epileptogenesis during development, presumably by altering the normal formation of neuronal networks (Manfredi et al, 2009).

Our aim is to identify which circuits are specifically involved in seizures, and whether the seizures are due to an imbalanced release of inhibitory and stimulatory neurotransmitters. Moreover, as recent data have shown that chronic nicotine treatment can improve some forms of ADNFLE, we will study the effect of chronic nicotine treatment on this mouse model.
nAChRs and neuroprotection

The hypothesis that nAChRs play a neuroprotective role during brain aging has received direct support from the studies showing that aged beta2 Ko mice are affected by region-specific structural alterations in cortical areas (including the loss of neocortical and hippocampal neurons, and astro- and microgliosis) and impaired cognitive performance.

Additional evidence for the neuroprotective effect of nicotinic agonists comes from in vivo and in vitro studies of animal models. Both in vivo and in culture cell, nicotine protects striatal, hippocampal and cortical neurons against the neurotoxicity induced by excitotoxic amino acids, as well as the toxicity caused by beta-amyloid, the major component of senile plaques.

It has been proposed that by activating nAChRs nicotine and nicotinic agents increase intracellular calcium, trophic factors and calcium binding protein levels and activate intracellular anti-apoptotic cascades. Our aim is to clarify the molecular mechanisms of nicotine-mediated neuroprotection, and we will analyse the effects of nicotine and nicotinic drugs on the different survival mechanisms.

nAChRs as new pharmacological targets

The evidence that nAChRs play a role in a number of different nervous functions and disorders has given impetus to the search for drugs that selectively affect different receptor subtypes.

Recent findings indicating that native receptors are much more heterogeneous than previously thought, and the fact that drug sensitivity may be species specific and vary from full to partial agonism or antagonism, has increased the complexity of studying drug specificity and opened up new possibilities for a pharmacological approach.

The discovery of new and selective nicotinic drugs is very important because of the preferential involvement of particular nAChR subtypes in many different diseases. Using traditional medicinal chemistry and the powerful new approach of combining 3D ligand binding site modelling with virtual drug discovery screening, in collaboration with the Institute of Medical Chemistry of the University of Milan and Genoa we have generated a number of ligands starting from the structure of epibatidine, cytisine, nicotine and alpha-conotoxins structure (reviewed in Gotti et al, 2006b; Tasso et al. 2009).

We have also used complementary approaches ranging from chemistry to molecular and cell biology and morphology, biochemistry and electrophysiology, and from in vitro functional assays to behavioural studies, to identify the effects of newly generated drugs as a means of unravelling the complexity of nAChR transmission in different neuronal pathways, and during the extreme life periods of development and aging.

This line of research has led to the formulation of new compounds including one recently patented alpha7 specific compound (European Patent N°2038281)

Our goal is to generate subtype specific agonist and antagonist drugs and allosteric modulators as lead compounds for the development of drugs capable of treating the diseases in which nAChRs are involved.

SELECTED PUBLICATIONS


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