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NICOTINIC RECEPTORS IN NEUROPSYCHIATRIC PATHOLOGIES OF ADULTHOOD AND DEVELOPMENTAL AGE.

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SUMMARY

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels present in many regions of the central nervous system (CNS) and the peripheral nervous system. The neuronal nicotinic acetylcholine receptors, being situated at the level of different neurotransmission pathways, participate in the function of many cerebral activities. Consequently, qualitative or quantitative deficits of nicotinic receptors are responsible for dysfunctions of these brain activities; such dysfunctions can occur at different stages of life due to brain aging or numerous neurological and psychiatric diseases of the developmental age, adulthood and old age. Modifications of specific nAChR subtypes have been found localized in specific brain regions in each such disorder.

In this review, we will discuss some of the above-mentioned brain disorders, reporting the relevant nAChR changes discovered to date, and summarize the therapeutic prospects currently under development.

Introduction

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels present in many regions of the central nervous system (CNS) and the peripheral nervous system. These receptors are pentamers which can be constituted by many different types of subunits, and can have multiple neuronal localizations (presynaptic, postsynaptic and nonsynaptic), in relation to their modulatory role within the neurotransmission process (e.g. presynaptic receptors increase the release of neurotransmitters from the presynaptic terminal; nonsynaptic receptors modify neuronal excitability of many neurotransmitter systems); moreover, it has also been shown that they are involved in synaptic plasticity (1; 2).

The neuronal nicotinic acetylcholine receptors, being situated at the level of different neurotransmission pathways, participate in the function of many cerebral activities. Consequently, qualitative or quantitative deficits of nicotinic receptors are responsible for dysfunctions of these brain activities that can occur in different stages of life, and be caused by brain aging or to numerous neurological and psychiatric diseases of the developmental age, adulthood and old age (1). Modifications of specific subtypes of nAChRs have been found localized in specific brain regions in each such disorder.

Decline, disruption or alterations of these receptors are reported in: neurodegenerative disorders like Parkinson's disease (PD), Alzheimer's disease (AD) and dementia with Lewy bodies; Tourette's syndrome; schizophrenia; depression; epilepsy; myasthenia; attention deficit hyperactivity disorder (ADHD); autism; Down syndrome; addiction; etc. As nAChRs are also present in some non-neuronal cells, they are not implicated in disorders of the nervous system only: for example, it has been shown that alpha7 nAChR (receptor sub-

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type which binds nicotine with low affinity) plays a role in lung cancer and heart disease (3).

Cognitive functions.

Regarding the influence of nicotinic receptors on cognitive functions, studies in animals and humans have established that nicotinic receptors modulate attention, learning and memory; confirming this, it has now been ascertained that nicotinic agonists improve these functions, while nicotinic antagonists impair them (4-10;).

Such modulation mainly occurs under specific conditions: in particular, when the subject is cognitively impaired or involved in a difficult task and the implementation of particular forms of attention, memory and learning is required (2; 11; 12). For example, the scientific literature reports that, in rats seeking food reward within a 16-arm radial maze, by infusing a nicotinic antagonist (methyllycaconitine) into brain areas involved with memory, such as the amygdala and the hippocampus, memory work worsened while reference memory or response latency remained unchanged (2; 11-14).

Several aspects of nAChR involvement in the physiology and pathophysiology of cognitive function are now under study: the brain areas affected, the subtypes of nAChRs involved (various subtypes are associated with different brain activities) and the interaction with other neurotransmitter systems (nAChRs also play a part in the transmission of other neurotransmitters) (7).

Brain aging and neurodegenerative disorders.

The nicotinic system has been implicated in brain aging mechanisms and neurodegenerative disorders. With the physiological aging of the brain, a reduction of different subtypes of nAChRs occurs in different brain regions, such as the hippocampus and the cerebral cortex; a similar process takes place in two of the most common forms of dementia: Alzheimer's disease and dementia with Lewy bodies (15). One of the early symptoms of AD is the impairment of hippocampus-based episodic memory function (16) and it has been shown that α7 nicotinic receptors of the hippocampus are impaired early in the course of AD (17).

It has also been shown that the accumulation of amyloid-β (Aβ) forms aggregates with α7 nAChRs in AD brain, causing a dysfunction of these receptors and a reduction in their numbers; this is one of the mechanisms by which the Aβ peptide leads to the dysfunction of the cholinergic system, that in turn contributes to the decline of cognitive functions in AD (2; 16, 17). All these data suggest that the decline of nicotinic mechanisms or loss of nAChRs could be involved in the neuronal degeneration associated with this disease.

Schizophrenia and ADHD.

Quantitative alterations of neuronal nAChRs have also been reported in postmortem brain tissue samples from schizophrenics; such alterations include a reduction of the density of the alpha7 receptor in several brain areas (18-22). Single nucleotide polymorphisms in the promoter region of the gene that codes for α7 nicotinic receptor (15q13- 14) have been associated with schizophrenia (21; 22).

While, as mentioned above, the receptor containing the α7 subunit plays a critical role in the diseases discussed so far, it probably has no relevance in another disease characterized by a decrease in the number of nicotinic receptors, the ADHD (23). Using an ADHD animal model (spontaneously hypertensive rat, SHR), Wigestrand and colleagues showed that the levels of α7 nAChRs are not compromised, while those of another receptor subtype, α4β2, do result compromised. This research group found that the number of central α4β2 diffusely decreased in the brain of the SHR and hypothesized that this may be the result of dysfunctional post-transcriptional regulation (24).

Epilepsy.

Finally, reviewing the information available to date on the relationship between the neuronal nicotinic acetylcholine receptor (NNR) system and human CNS pathologies, we cannot fail to mention that the first human disease which was discovered to be associated with a neuronal nAChR was a form of epilepsy (autosomal dominant nocturnal frontal lobe epilepsy, ADNFLE), which may arise from a mutation in the genes coding for the α4 or β2 subunits; these mutations increase receptor

sensitivity for ACh and, consequently, in some way contribute to determining an abnormal neuronal synchronization, causing seizures (2; 25-36).

Future prospects.

In the light of what is reported above, as well as further experimental evidence, the current therapeutic objective for neurodegenerative disorders, schizophrenia, ADHD, etc., is to increase nicotinic receptor function, in order to accomplish three main aims: protection against neurodegeneration, improvement of cognitive function and reduction of the negative and positive psychotic symptoms.

The beneficial role of nAChR activation is also supported by numerous scientific studies: according to epidemiological surveys, cigarette smokers are protected against the development of neurodegenerative disorders, such as PD and, according to some studies, in AD (37, 38); nicotine is considered to be a neuroprotective agent, since it staves off neuronal death both *in vitro* and *in vivo* (38); nicotine has also been shown to increase cognition in schizophrenic patients (21) and, perhaps as a consequence, the incidence of tobacco dependence is higher in schizophrenics than in the healthy population (18, 20); the percentage of adolescents and adults with ADHD who smoke is two times higher than that of normal subjects of the same age, and this is probably linked to the beneficial effects of nicotine on cognitive deficits, especially attention, which are an important component of the disease, particularly so in adolescents and adults (10, 39, 40, 41).

Despite these positive properties, nicotine cannot be used as a therapy because of its adverse effects (38, 39). Consequently, alternative molecules that activate nAChRs with a better safety/tolerability profile are being developed as new therapeutic agents for these disorders (15-17; 19; 21; 27; 42).

In contrast with preclinical results, suggesting that selective nicotinic agonists (that excite, for example, the $\alpha 7$ and $\alpha 4\beta 2$ subtypes) represent an effective treatment in animal models of neurodegenerative disease and schizophrenia, current clinical stages of development of these potential therapeutic drugs are not convincing (22; 43; 44). Some problems associated with the clinical development are related to dose-limiting adverse effects caused by low subtype selectivity (43). To overcome these limits, researchers are now conducting *in vivo* studies of allosteric activators, which include allosteric agonists and allosteric modulators of specific nAChR subtypes and have been found to be more selective (43; 45). However, further research is still needed to determine the efficacy and safety of these innovative nicotinic treatments (7; 13).

One drug influencing cerebral nAChRs that is already clinically employed is galantamine (Reminyl). It is an acetylcholinesterase inhibitor prescribed for AD, also capable of potentiating nAChRs, probably by binding to an allosteric site of the receptor. Regarding ADHD, nicotinic agonists have proven to be efficient both in preclinical animal trials and in humans. In particular, two $\alpha 4\beta 2$ agonists (ABT-089 and ABT-418) improve cognitive deficits in adults with this disorder; furthermore, studies have indicated that they also enhance the expression of this receptor subtype (39; 46; 47).

Conclusions.

Additional studies are needed on the pathophysiologic mechanisms that involve the cholinergic-nicotinic system in neurological and psychiatric pathologies of developmental and adult age, and on therapeutic substances that can affect them. However, the data included in this review provide researchers with theoretical and practical bases to better understand the pathogenesis of these diseases and the therapeutic use of nAChR agonists.

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