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Nicotinic acetylcholine receptors in human genetic disease

Christian P. Schaaf, MD, PhD[1,2]

Nicotinic acetylcholine receptors represent a family of ligand-gated ion channels that are widely expressed in the central and peripheral nervous systems. To date, 16 genes encoding subunits of mammalian nicotinic acetylcholine receptors have been identified. The various subunits form homomeric or heteromeric receptor proteins, allowing for a complex and adaptable system of nicotinic neurotransmission. Mutations of nicotinic receptor genes can cause Mendelian disorders, most importantly congenital myasthenic syndromes, multiple pterygium syndromes, and nocturnal frontal lobe epilepsies. Haploinsufficiency of *CHRNA7* predisposes to neuropsychiatric phenotypes in 15q13.3 deletion syndrome. The role of various nicotinic receptor genes is also discussed for complex disorders such as addiction, schizophrenia, Alzheimer disease, and Parkinson disease.

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Acetylcholine is an essential neurotransmitter in the central and peripheral nervous systems. Its signal can be transduced by two different types of receptors, which are classified by their sensitivity to either muscarine or nicotine. Muscarinic acetylcholine receptors are family-A G-protein-coupled receptors, whereas nicotinic acetylcholine receptors are ligand-gated ion channels.[1,2] Muscarinic receptors are widely recognized for their role in the parasympathetic nervous system. Their signals are relatively slow and evolve over seconds to minutes. Nicotinic receptors, on the other hand, mediate fast synaptic transmission in millisecond time frames. They are critical to development and synaptic plasticity, and they participate in learning, memory, and attention. The major cholinergic nuclei of the mammalian brain are located in the basal forebrain, from which they project throughout the cortex and the hippocampus. Cholinergic nuclei of the brain stem, in particular the pedunculopontine nucleus and the laterodorsal tegmental nucleus, provide widespread innervation to the thalamus and the midbrain. Cholinergic interneurons control excitatory input in the striatum, and they are important terminal zones of dense dopaminergic projections in the nucleus accumbens.[2,3] Acetylcholine is released into the synaptic cleft, but also at nonsynaptic sites. Activation of presynaptic nicotinic receptors causes enhanced neurotransmitter release, whereas postsynaptic nicotinic acetylcholine receptors contribute to fast excitatory transmission. Nonsynaptic nicotinic acetylcholine receptors contribute to diffuse volume transmission, thereby influencing neuronal excitability and modulating various neurotransmitter systems.[2] Release of acetylcholine is episodic and in a pulsed manner. Depending on presence, abundance, and timing of acetylcholine binding, nicotinic acetylcholine receptors can adopt one of three functional states: closed at rest, open pore, and closed desensitized.[2] Prolonged exposure to low doses of acetylcholine, nicotine, or a nicotinic agonist will cause significant desensitization, which stabilizes the receptor in the closed state, unresponsive to further agonist stimulation.[4] This needs to be considered when discussing therapeutic interventions in disorders of nicotinic acetylcholine receptors.

Nicotinic acetylcholine receptors are assembled from five transmembrane subunits, which are arranged around a central water-filled pore. To date, 16 distinct subunits of nicotinic acetylcholine receptors have been identified in the human proteome, of which 11 are neuronal (α2–7, α9, α10, β2–4) and 5 are muscular (α1, β1, γ, δ, and ε). The respective human genes are *CHRNA1–7*, *CHRNA9*, *CHRNA10*, *CHRNB1–4*, *CHRNG*, *CHRND*, and *CHRNE*. There are two subtypes of the muscular nicotinic acetylcholine receptor: $(\alpha1)_2\beta1\delta\gamma$, which represents the fetal form, and $(\alpha1)_2\beta1\delta\varepsilon$, which represents the adult form. During development, the former is gradually replaced by the latter. Therefore, mutations in *CHRNG* cause phenotypes of congenital manifestation, whereas mutations in *CHRNE* manifest postnatally. The diversity of nicotinic acetylcholine receptors in the human brain is significant, due to the combinatorial effects of subunit assembly in heteropentameric receptors. Several different subtypes can be expressed within the same tissue or even within the same cell. Only two subunits (α7 and α9) are known to form homopentameric nicotinic acetylcholine receptors, of which only α7 is abundantly expressed and distributed in the human brain. Neuronal heteropentamers are formed by two α units (α2–6) and three β units (β2–4). Heteropentameric receptors have two acetylcholine-binding sites, which are located between the α and β subunits each.

[1]Baylor College of Medicine, Department of Molecular and Human Genetics, Houston, Texas, USA; [2]Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, Texas, USA. Correspondence: Christian P. Schaaf (schaaf@bcm.edu)

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Homopentameric receptors have five binding sites, one at each interface between two subunits.[2,5]

To date, 9 of the 16 human nicotinic acetylcholine receptor genes have been associated with Mendelian disorders. An overview is provided in **Table 1**.

CONGENITAL MYASTHENIC SYNDROMES

Congenital myasthenic syndromes (CMSs) are a group of genetically determined disorders characterized by dysfunction of neuromuscular transmission, clinically manifesting as muscular weakness that worsens with exertion, and strength returning

Table 1 Monogenic disorders of human nicotinic acetylcholine receptor genes

Gene	Location[a]	Mendelian disorder(s)	Inheritance pattern	Mutation type(s)	(Proposed) mechanism	Reference(s)
CHRNA1	2q31.1	Congenital myasthenic syndrome (slow-channel), OMIM 601462	Autosomal dominant	Missense	Gain of function	40–43
		Congenital myasthenic syndrome (fast-channel), OMIM 608930	Autosomal recessive	Missense	Loss of function	44–46
			Autosomal dominant	Missense	Loss of function	47
		Lethal multiple pterygium syndrome, OMIM 253290	Autosomal recessive	Nonsense	Loss of function	48
CHRNA2	8p21.2	Nocturnal frontal lobe epilepsy, type 4, OMIM 610353	Autosomal dominant	Missense	Gain of function	49
CHRNA3	15q25.1	None	N/A	N/A	N/A	N/A
CHRNA4	20q13.33	Autosomal dominant nocturnal frontal lobe epilepsy, type 1, OMIM 600513	Autosomal dominant	Missense, indel	Gain of function, loss of function	50–52
CHRNA5	15q25.1	None	N/A	N/A	N/A	N/A
CHRNA6	8p11.21	None	N/A	N/A	N/A	N/A
CHRNA7	15q13.3	15q13.3 microdeletion syndrome, OMIM 612001	Autosomal dominant (semidominant)	Whole-gene deletion	Haploinsufficiency	15–18,22,24
CHRNA9	4p14	None	N/A	N/A	N/A	N/A
CHRNA10	11p15.4	None	N/A	N/A	N/A	N/A
CHRNB1	17p13.1	Congenital myasthenic syndrome (slow-channel), OMIM 601462	Autosomal dominant	Missense	Gain of function	40,53
		Congenital myasthenic syndrome associated with acetylcholine receptor deficiency, OMIM 608931	Autosomal recessive	Indel, exon skipping	Loss of function	54
CHRNB2	1q21.3	Nocturnal frontal lobe epilepsy, type 3, OMIM 605375	Autosomal dominant	Missense	Gain of function	55,56
CHRNB3	8p11.21	None	N/A	N/A	N/A	N/A
CHRNB4	15q25.1	None	N/A	N/A	N/A	N/A
CHRND	2q37.1	Lethal multiple pterygium syndrome, OMIM 253290	Autosomal recessive	Nonsense, missense	Loss of function	48
		Congenital myasthenic syndrome (fast-channel), OMIM 608930	Autosomal recessive	Missense, indel	Loss of function	45,57
		Congenital myasthenic syndrome (slow-channel), OMIM 601462	Autosomal dominant	Missense	Gain of function	58
CHRNE	17p13.2	Congenital myasthenic syndrome associated with acetylcholine receptor deficiency, OMIM 608931	Autosomal recessive	Nonsense, missense, indel, splice site, promoter	Loss of function	40,59–66
		Congenital myasthenic syndrome (fast-channel), OMIM 608930	Autosomal recessive	Missense	Loss of function	67–70
		Congenital myasthenic syndrome (slow-channel), OMIM 601462	Autosomal dominant	Missense	Gain of function	40,67,71,72
		Congenital myasthenic syndrome (slow-channel), OMIM 601462	Autosomal recessive	Indel, missense	Uncertain	72
CHRNG	2q37.1	Escobar syndrome, OMIM 265000	Autosomal recessive	Missense, indel, nonsense	Loss of function	73,74
		Lethal multiple pterygium syndrome, OMIM 253290	Autosomal recessive	Exon deletion, indel	Loss of function	74

Indel, insertions/deletions.
[a]Based on UCSC genome browser (GRCh/hg19).

(at least partially) after resting.[6] Depending on the localization of the mutated protein, CMSs are classified into four categories: (i) presynaptic compartment CMS, (ii) synaptic basal lamina–associated CMS, (iii) postsynaptic compartment CMS, and (iv) CMS caused by deficient protein glycosylation. Postsynaptic disorders can be divided into two kinetic defects, fast-channel (OMIM 608930) and slow-channel (OMIM 601462) CMSs, and a third disorder, CMS with acetylcholine receptor deficiency (OMIM 608931). Mutations in genes encoding nicotinic acetylcholine receptors (*CHRNA1*, *CHRNB1*, *CHRND*, and *CHRNE*) are considered postsynaptic compartment CMSs and are responsible for up to 60% of all cases (**Table 1**).[7] Deficient clustering of acetylcholine receptors at the end plate can be caused by mutations in *MUSK*, *RAPSN*, or *DOK7*, and others, causing CMSs with acetylcholine receptor deficiency and abnormal synaptic differentiation.[7] The single most common gene causing CMS is *CHRNE*, accounting for 20–25% of all cases, and 50% of those in which a molecular diagnosis can be established.[7] In slow-channel CMSs, gain-of-function mutations cause prolonged activations of the nicotinic acetylcholine receptors. These usually follow autosomal dominant inheritance. Treatment consists of long-acting open-channel blockers fluoxetine and quinidine; however, the efficacy and tolerability features of these medications are limited.[6] In fast-channel CMSs, receptor activations are brief because acetylcholine receptors do not stay open long enough. These are usually caused by loss-of-function mutations and follow autosomal recessive inheritance. Fast-channel CMS is treated with acetylcholine esterase inhibitors and 3,4-diaminopyridine.[6] The most common type of CMS, i.e., CMS associated with acetylcholine receptor deficiency, may or may not have minor kinetic abnormalities. The causative mutations involve loss of function, and the inheritance pattern is autosomal recessive. The affected individuals respond favorably, but incompletely, to acetylcholine esterase inhibitors. Additional use of 3,4-diaminopyridine may result in further improvement, in particular by increasing endurance.[8]

MULTIPLE PTERYGIUM SYNDROMES

Multiple pterygium syndromes are a group of disorders clinically characterized by the presence of joint contractures (arthrogryposis) and pterygia (skin webbing across joints, e.g., neck, elbows, knees), frequently accompanied by additional congenital anomalies.[9] Loss-of-function mutations in the muscular nicotinic acetylcholine receptor genes *CHRNA1*, *CHRND*, and *CHRNG* have been identified as the causes of multiple pterygium syndromes, following recessive inheritance (**Table 1**). One could conceive that homozygous or compound heterozygous mutations in *CHRNB1* may cause multiple pterygium syndrome, but no such case has been reported in the literature to date. Mutations in *CHRNE*, which is only expressed in the late fetal, perinatal, and postnatal periods, would not be expected to cause a severe congenital phenotype such as that seen in multiple pterygium syndromes.

Lethal (OMIM 25390) and nonlethal (OMIM 265000, Escobar variant) forms of multiple pterygium syndromes exist. Mutations in *CHRNA1*, *CHRND*, and *CHRNG* have been reported as the causes of the lethal type. On the other hand, mutations of *CHRNG* are the only known cause of the nonlethal Escobar variant to date. The phenotype of Escobar syndrome is caused by the transient inactivation of the neuromuscular end plate, quite similar to the symptoms found in neonates with congenital arthrogryposis who were exposed to maternal acetylcholine receptor antibodies during fetal development. Because *CHRNG* gene expression is restricted to early development (before the 33rd week of gestation in humans), patients with Escobar syndrome do not manifest myasthenic symptoms later in life, which is a major difference from disorders caused by mutations in other acetylcholine receptor subunits. The treatment of Escobar syndrome is symptomatic. Early surgical intervention is recommended to prevent progression of deformity and a decrease in pulmonary capacity, especially if scoliosis is severe. Orthopedic therapy with splinting combined with vigorous physical therapy is critical, to increase joint mobility and to decrease muscle atrophy.

AUTOSOMAL DOMINANT NOCTURNAL FRONTAL LOBE EPILEPSY

Nocturnal frontal lobe epilepsies (OMIM 600513, OMIM 605375, OMIM 610353, and OMIM 615005) are a group of idiopathic partial epilepsies characterized by clustered attacks of brief motor seizures, mostly occurring during non–rapid eye movement sleep.[10] The age of onset is usually during childhood or adolescence, although this may vary considerably, even within the same family. The motor manifestations are often stereotyped and consist of brief stiffening of the limbs, accompanied by dystonic movements of neck, arms, and legs. Grunting sounds, vocalizations, and difficulty in breathing can occur with the seizures, and sleepwalking has been reported. Parasomnias, which are nonepileptic events with similar clinical presentation, are the most important differential diagnosis. Mean seizure frequency in autosomal dominant nocturnal frontal lobe epilepsy is about 20 per month. More than 90% of nocturnal frontal lobe seizures arise during sleep, and although about one-third of patients with nocturnal frontal lobe epilepsy may have seizures during the awake state, these are rare (less than 10 per year) and are usually confined to childhood and adolescence.

Mutations in *CHRNA2*, *CHRNA4*, and *CHRNB2* have been found to cause autosomal dominant nocturnal frontal lobe epilepsy (**Table 1**). All mutations reported to date are missense mutations or indels (insertions/deletions) and usually affect the transmembrane domains or very nearby domains of the respective proteins, thereby affecting the kinetics of the ion pore. Mutations in *CHRNA2* and *CHRNB2* are usually gain-of-function mutations, leading to increased sensitivity to acetylcholine or retardation of desensitization of the receptor. For *CHRNA4*, mutations can either be either gain-of-function (increased affinity to acetylcholine) or loss-of-function (acceleration of desensitization and decreased calcium permeability) types.[10] Mutations in one non-nicotinic receptor gene, *KCNT1*,

have been found to be a cause of severe autosomal dominant nocturnal frontal lobe epilepsy with behavioral or psychiatric problems and intellectual disability.[11]

Inheritance of all nocturnal frontal lobe epilepsies is autosomal dominant, and the estimated penetrance is high (70–80%), however with variable clinical expressivity. Some of the reported mutations not only cause epilepsy but also can be associated with additional neurological and psychiatric features. Examples are the p.259insL mutation in *CHRNA4*, which not only causes nocturnal seizures, but also psychiatric disease, in particular schizophrenia, and the p.I312M mutation in *CHRNB2*, which not only causes seizures but also distinct cognitive impairments.[5]

The seizures of nocturnal frontal lobe epilepsy are usually relatively benign, as they occur during sleep and, in most cases, respond very well to treatment with antiepileptic medications. Carbamazepine has been shown to be efficacious in about two-thirds of cases, greatly reducing seizure frequency and complexity. A single dose at bedtime is usually sufficient. Other reported treatments of nocturnal frontal lobe epilepsy include topiramate, oxcarbazepine, and transdermal nicotine patch.[10] About 30% of cases with nocturnal frontal lobe epilepsy are resistant to antiepileptic drugs. Surgical intervention might have an indication in these nonresponders. Whether there are specific genotypes causing nonresponsiveness to treatment in nocturnal frontal lobe epilepsy remains unclear at this time.

NEUROPSYCHIATRIC PHENOTYPES AND COPY NUMBER VARIATIONS OF *CHRNA7*

The α7 subunit is unique in that it forms functional homopentameric receptors that are abundantly expressed in the human brain. Structurally, α7 is thought to be the closest to the most ancient forms of nicotinic receptors that evolved millions of years ago and seems to have preserved specific functionalities, such as high calcium permeability and certain toxin sensitivity (e.g., α-bungarotoxin).[12] The human *CHRNA7* gene is located on chromosome 15q13.3, in one of the most unstable regions of the human genome. Proximal 15q (15q11-q14) is rich in low-copy repeats. DNA copy number variations of the region include deletions, pericentric and paracentric inversions, duplications, triplications, translocations, and supernumerary inv dup(15) chromosomes.[13] Break points of these rearrangements are located within complex sets of low-copy repeats named break point 1 (BP1) to BP6. The *CHRNA7* gene is located between BP4 and BP5, which have been proposed to mediate most of the rearrangements involving *CHRNA7*. They are constituted by a complex set of large duplicated segments with >99% identity, positioned in opposite directions relative to each other. A paracentric inversion between BP4 and BP5 is frequently found in various populations. A small inversion within a portion of BP4 has been postulated to put segments of BP4 and BP5 in direct orientation relative to each other, which, in turn, can predispose to nonallelic homologous recombination, resulting in recurrent reciprocal BP4–BP5 microdeletions and microduplications. Additional, smaller low-copy repeats within the BP4–BP5 segment play a role in the etiology of smaller copy number variants involving the *CHRNA7* gene. In fact, at least six different classes of microduplications, varying in size from 350 kb to 1.6 Mb, have been shown to arise involving preexisting heterogeneous inverted BP4–BP5 chromosomes.[13]

Chromosome 15q13.2 also harbors the chimeric *CHRFAM7A* gene, which is a partial duplication of *CHRNA7* (exons 5–10) forming a hybrid with a novel gene from the family with sequence similarity 7 (*FAM7A*). The *FAM7A* part consists of four exons (named D, C, B, and A), of which three (C, B, A) arose from a partial duplication of *ULK4* (a serine/threonine kinase on chromosome 3p22) and one (D) is of unknown provenance. The *CHRFAM7A* gene is human specific and is located on 15q13.2, only 1.6 Mb centromeric to *CHRNA7,* transcribed in opposite direction. It is expressed in multiple tissues, including brain, although less abundantly than *CHRNA7*. Copy number of *CHRFAM7A* is highly variable in humans. Although most individuals have one or two copies of *CHRFAM7A*, some have zero and some have three copies. The CHRFAM7A protein has been proposed to be a dominant negative regulator of the α7 nicotinic acetylcholine receptor.[14]

CHRNA7 deletions

Heterozygous microdeletions between BP4 and BP5 on chromosome 15q13.2q13.3 including *CHRNA7* (OMIM 612001) were first reported in 2008 as a cause of intellectual disability and seizures[15–18] and then were also found to be overrepresented in cohorts of individuals with schizophrenia.[19,20] The deletion is found in ~1% of individuals with idiopathic generalized epilepsy.[21] These deletions affect a total of six genes in the National Center for Biotechnology Information's Reference Sequence database (RefSeq)—*MTMR15*, *MTMR10*, *TRPM1*, *KLF13*, *OTUD7A*, and *CHRNA7*—as well as a microRNA gene, *hsa-mir211*. Based on expression patterns and function, haploinsufficiency of *CHRNA7* had been considered the probable cause of BP4–BP5 deletion syndrome, which was then substantiated by the identification of individuals with much smaller deletions affecting only *CHRNA7* and the first exon of a noncoding RNA variant of *OTUD7A*.[22] The affected individuals manifest phenotypes highly similar to those seen in BP4–BP5 deletion syndrome, i.e., developmental delay, intellectual disability, and seizures. Deletions including *CHRNA7* are not found in control cohorts and therefore appear to have complete penetrance.[23] This is only questioned by a few reports of individuals with rare homozygous or compound heterozygous deletions involving *CHRNA7*, for whom parents heterozygous for the deletion are reported as healthy with normal intelligence and no history of psychiatric disorder.[24] One might conclude that the penetrance for neuropsychiatric phenotypes in individuals with deletion of *CHRNA7* is high, but not quite 100%. Homozygous or compound heterozygous deletions of *CHRNA7* cause a phenotype of neonatal encephalopathy, with severe hypotonia, cortical visual impairment, profound developmental and intellectual impairment, and intractable epilepsy.[24–26]

CHRNA7 duplications

Duplications reciprocal to the BP4–BP5 deletions were first described by van Bon[18]; however, due to the small number of patients reported, it was difficult to conclude whether this microduplication actually contributes to the etiology of neurodevelopmental phenotypes. Szafranski et al.[13] then reported four additional BP4–BP5 duplication cases and 55 smaller *CHRNA7* duplications that had been identified by clinical chromosome microarray analysis. They went on to describe two different classes of BP4–BP5 duplications and five classes of small *CHRNA7* duplications, based on size differences and break points. Clinical data were available for 11 probands and their families and suggested an overrepresentation of developmental delay/intellectual disability, muscular hypotonia, and a variety of neuropsychiatric disorders among the affected individuals. However, it was noticed that the small *CHRNA7* duplications are seen at high frequency not only among affected individuals, but also in control cohorts, so it was concluded that the clinical significance of these microduplications was uncertain.[13] In fact, there are at least five studies published to date that tested the prevalence of *CHRNA7* duplications in control populations,[21,27–30] with a total prevalence of 134 *CHRNA7* duplications in 24,980 individuals (for a frequency of 1 in 186). The prevalence of small *CHRNA7* duplications among all samples submitted for clinical chromosome microarray analysis is 185 in 32,212 (1 in 174),[13,27] which is not a difference of statistical significance when compared with the prevalence among controls (one-tailed *P* value of 0.2922 in a χ^2 test with Yates correction). Significant enrichment of the small *CHRNA7* duplications was, however, shown among individuals with attention deficit hyperactivity disorder, with an odds ratio of 2.22 (a total of 34 individuals with *CHRNA7* duplication among 3,003 individuals total, for a frequency of 1 in 88).[28] In summary, based on current data, the role and significance of *CHRNA7* duplications in the etiology of neuropsychiatric disease is limited. It has not yet been determined whether duplication of *CHRNA7* causes actual overexpression of the α7 nicotinic acetylcholine receptor, in particular in human brain. No studies have investigated whether *CHRNA7* duplication changes the electrophysiology, connectivity, or function of the human brain. One might speculate that copy number of *CHRFAM7A* could have a modifying effect, such that an increasing copy number of *CHRFAM7A* decreases the effect of increasing copy number of *CHRNA7*. The high frequency of *CHRNA7* duplications in the general population would make them a common risk factor for behavioral and neuropsychiatric phenotypes should there be enough evidence for a true pathological effect.

COMPLEX DISORDERS

The involvement of nicotinic acetylcholine receptors is being discussed in several other disorders, mostly common disorders of complex inheritance and multifactorial etiology. Four (groups of) disorders worth discussing are schizophrenia, addiction, Alzheimer disease, and Parkinson disease.

Schizophrenia

It is well known that individuals with schizophrenia have a much higher prevalence of smoking (90%) when compared with the general population (33%).[31] Individuals with schizophrenia have a small, but significant and reproducible, decrease in ^{125}I-α-bungarotoxin–binding sites and α7 immunoreactivity in the hippocampus, reticular nucleus of the thalamus, and the cingulate and frontal cortex.[31] In addition, sensory gating by p50 auditory evoked potentials is deficient among many individuals with schizophrenia and has been mapped to 15q13-14 by linkage, the locus that contains the *CHRNA7* gene.[32] Polymorphisms in the promoter of *CHRNA7* have been associated with schizophrenia and diminished p50 sensory gating.[33,34] Nicotine has been shown to transiently reverse p50 deficits,[32] and, more importantly, a selective α7 partial agonist, EVP-6124, has been shown to have clinically meaningful effects on global cognitive function, negative symptoms, and general clinical function in individuals with schizophrenia.[35]

Addiction

The addictive effects of nicotine are at least in part mediated via α4β2-containing nicotinic acetylcholine receptors, which cause increases in mesolimbic dopamine release leading to nicotine dependence.[12] In addition, nicotinic acetylcholine receptors can modulate the release of many other neurotransmitters and mediate the neuronal mechanisms associated with development and maintenance of drug addiction. There is high comorbidity of nicotine and alcohol dependence, which at least in part is explained by common underlying cholinergic mechanisms. In particular, the *CHRNA5/A3/B4* cluster on chromosome 15q25.1 has been associated with both nicotine and alcohol dependence. For other drug dependencies data are much more limited, and although the cholinergic system has been shown to play a role in several aspects of cocaine dependence in various animal studies, there is a relative lack of human data, and the contributions of specific nicotinic receptors are yet to be elucidated.[12]

Alzheimer disease

The most well-appreciated loss of neurons in brains of people with Alzheimer disease is that of the cholinergic system, in particular the basal forebrain cholinergic neurons.[36] The decline of cortical cholinergic activity correlates with the severity of Alzheimer symptoms and intellectual deterioration. Along with clinical progression, the number of nicotinic acetylcholine receptors decreases, especially in the hippocampus and cortex.[37] In addition, a role for α4 and α7 has been suggested in the accumulation of β amyloid peptide and hyperphosphorylated tau.[38] The most commonly prescribed drugs for Alzheimer disease are acetylcholine esterase inhibitors. But nicotinic agonist agents also are increasingly shown to improve cognitive deficits in Alzheimer disease patients.[12]

Parkinson disease

The motor symptoms of Parkinson disease result from a degeneration of dopaminergic neurons in the nigrostriatal pathway.

Nicotinic acetylcholine receptors are important in promoting the release of dopamine in this pathway, in particular α6β3β2 and α4β2 receptors, which facilitate the release of dopamine from nerve endings in the striatum.[31] A decrease of nicotinic acetylcholine receptors has been found in the cerebral cortex of Parkinson disease patients and is mainly attributed to a decrease in α4- and α7-containing receptors. Finally, epidemiological studies show that smoking is associated with a lower incidence of Parkinson disease.[39] Not surprisingly, nicotine and nicotinic receptor agonists are being investigated as promising therapeutic agents in the management of Parkinson disease.[12]

THERAPEUTIC CONSIDERATIONS

As outlined in some of the above sections, disorders of nicotinic acetylcholine receptors have promising therapeutic potential that goes well beyond symptomatic treatment but exploits a more fundamental understanding of disease mechanisms and neuropharmacology. Nicotinic agonist drugs are currently approved and marketed for smoking cessation and in advanced clinical trials for depression, attention deficit hyperactivity disorder, schizophrenia, Alzheimer disease, and Parkinson disease.[12] With dramatic advances in our understanding of the exact genetic causes of disorders of nicotinic acetylcholine receptors, along with increasing knowledge of what the respective genetic mutations and alterations do on a (patho)physiological level, there is hope that rational molecular therapies are actually within reach. The interest of the pharmacological industry in common disorders such as Alzheimer disease, Parkinson disease, and nicotine addiction will also prove to be beneficial for the much more rare orphan diseases caused by deficient nicotinic signaling.

The promiscuity of the nicotinic acetylcholine receptor system represents a major challenge to the development of respective compounds. Many have failed in clinical trials, either due to lack of efficacy or due to side effects, resulting in unacceptably narrow therapeutic windows. There is great need for drugs that have an optimal combination of pharmacodynamics (potency and selectivity) and pharmacokinetics (absorption, penetration across the blood–brain barrier, and protein binding) to preferentially target a given nicotinic acetylcholine receptor subtype with doses that would be inefficient at other receptor subtypes, to minimize side effects.[12] Beyond nicotinic agonists, positive allosteric modulators are getting increasing attention because they lack the intrinsic activity and only become active in the presence of acetylcholine, causing a potentiation of its effect. Allosteric binding sites are topographically distinct from agonist binding sites, are less conserved, and differ among nicotinic receptor subtypes, so that selectivity for positive allosteric modulators can be achieved much more easily than for cholinergic agonist drugs. Combination strategies of agonists plus positive allosteric modulators may be particularly attractive whenever a decreased number of functional receptors is present because some positive allosteric modulators may oppose agonist-induced desensitization.[2,12]

In summary, the importance of nicotinic acetylcholine receptors is increasingly recognized in the field of neurological, behavioral, psychiatric, and neurodegenerative disorders. There is tremendous potential for the development and implementation of targeted therapies for both the rare, monogenic Mendelian disorders of nicotinic acetylcholine receptor genes, and the more common, genetically complex diseases manifesting decreased cholinergic signaling.

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DISCLOSURE

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