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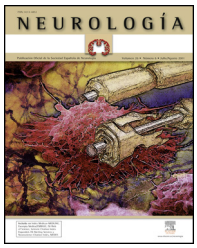

REVIEW ARTICLE

Cholinergic markers in the cortex and hippocampus of some animal species and their correlation to Alzheimer's disease☆

E. Orta-Salazar[a], C.A. Cuellar-Lemus[a], S. Díaz-Cintra[b], A.I. Feria-Velasco[a,*]

[a] *Centro Universitario de Ciencias Biológicas y Agropecuarias (CUCBA), Universidad de Guadalajara, Zapopan, Mexico*
[b] *Instituto de Neurobiología (INB), Campus UNAM-Juriquilla, Juriquilla, Querétaro, Mexico*

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KEYWORDS
Cholinergic innervation;
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Cerebral cortex;
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Abstract
Introduction: The cholinergic system includes neurons located in the basal forebrain and their long axons that reach the cerebral cortex and the hippocampus. This system modulates cognitive function. In Alzheimer's disease (AD) and ageing, cognitive impairment is associated with progressive damage to cholinergic fibres, which leads us to the cholinergic hypothesis for AD.
Development: The AD produces alterations in the expression and activity of acetyltransferase (ChAT) and acetyl cholinesterase (AChE), enzymes specifically related to cholinergic system function. Both proteins play a role in cholinergic transmission, which is altered in both the cerebral cortex and the hippocampus due to ageing and AD. Dementia disorders are associated with the severe destruction and disorganisation of the cholinergic projections extending to both structures. Specific markers, such as anti-ChAT and anti-AChE antibodies, have been used in light immunohistochemistry and electron microscopy assays to study this system in adult members of certain animal species.
Conclusions: This paper reviews the main immunomorphological studies of the cerebral cortex and hippocampus in some animal species with particular emphasis on the cholinergic system and its relationship with the AD.

PALABRAS CLAVE
Inervación colinérgica;
Colina acetiltransferasa;
Acetilcolinesterasa;

Marcaje colinérgico en la corteza cerebral y el hipocampo en algunas especies animales y su relación con la enfermedad de Alzheimer

Resumen
Introducción: El sistema colinérgico incluye neuronas localizadas en el cerebro basal anterior y sus axones largos proyectan a la corteza cerebral e hipocampo. Este sistema modula la función cognitiva. En la enfermedad de Alzheimer (EA) y en el proceso de envejecimiento la disfunción

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* Corresponding author.
E-mail address: alfredoferia1340@hotmail.com (A.I. Feria-Velasco).

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Corteza cerebral;
Hipocampo;
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colinérgica hay una asociación entre el deterioro cognitivo y el daño progresivo de las fibras colinérgicas, lo que conduce al postulado de la hipótesis colinérgica.
Desarrollo: En la EA se producen alteraciones en la expresión y en la actividad de la colina acetiltransferasa (ChAT) y la acetilcolinesterasa (AChE), enzimas específicas relacionadas con la función del SC. Ambas proteínas juegan un papel importante en la transmisión colinérgica mostrando variaciones en la corteza cerebral y en el hipocampo, tanto por el envejecimiento, como por la EA. En ambas estructuras, los desórdenes demenciales están asociados a la destrucción severa y desorganización de las proyecciones colinérgicas que se encuentran afectadas. Para el estudio de este sistema se han usado marcadores específicos como los anticuerpos contra ChAT y AChE que han sido empleados en las técnicas de inmuhistoquímica de luz y microscopia electrónica en algunas especies animales.
Conclusiones: En este trabajo se hace una revisión de los principales estudios inmunomorfológicos de la corteza cerebral e hipocampo de varias especies animales con énfasis en el SC y su relación con la EA.

Introduction

In mammalian brains, the cholinergic nuclei are located in the basal forebrain (BF), from the medial septum along the diagonal band of Broca to the nucleus basalis of Meynert (NBM) including the substantia innominata. The more rostral neurons located in the medial septum and vertical limb of the diagonal band of Broca innervate the hippocampus (via the hippocampal septum). More caudal neurons, including the NBM and substantia innominata, innervate the cerebral cortex and amygdala. Nuclei in the BF receive reciprocal connections from limbic structures (orbitofrontal, temporal pole, medial region of the temporal lobe, and entorhinal cortex). Brainstem nuclei (the pedunculopontine, tegmental, and lateral dorsal tegmental nuclei) activate the cerebral cortex by means of projections to the thalamus. Both the BF and the brainstem project to the thalamic reticular nucleus; cholinergic nuclei significantly influence limbic and cortical activity both directly and indirectly. Neurotransmission in the cholinergic system (CS) is involved in such processes as memory, learning, sleep, and other functions.[1] Problems with neurotransmission elicit changes in these functions and this may be one of the causes of senile dementia or Alzheimer disease (AD). Biosynthesis of acetylcholine ($C_7H_{16}NO_2$) or ester of ascetic acid and choline takes place in the cytoplasm of the soma and in presynaptic terminals by means of the activity of the choline acetyltransferase enzyme (ChAT). In the synaptic cleft, it is broken down into acetate and choline by the acetylcholinesterase enzyme (AChE) for reuptake by the presynaptic neuron.[2,3] Both ChAT and AChE are proteins that function as specific markers of physiological activity by cholinergic neurons. Additionally, both play an important role in the homeostasis of neuronal acetylcholine.[4]

Cholinergic metabolism dysfunction has been reported in AD,[3,5,6] as well as neuronal changes in the acetylcholine innervation, synthesis, breakdown, and reuptake. In humans, the decrease in cholinergic cells reflects a pathological change in the basal forebrain.[7–11] Although this is not counted as one of the initial events in AD or the ageing process,[12] it does imply cortical denervation related to the elimination of extrinsic projections to the cerebral cortex.[6] This situation manifests as cognitive, intellectual, and social dysfunction according to the AD progression pattern and with the following symptoms: agitation, psychosis, depression, apathy, anxiety, sleep disorders, and appetite disorders.[12–15] These patients exhibit decreased production of ChAT and AChE in the cerebral cortex and hippocampus, as well as impairment in axonal transport of those enzymes, due to degeneration of cholinergic neurons in the basal forebrain (NBM).[16] In quantitative studies, brain tissue in patients with AD displayed a 55% decrease in reactive cholinergic fibres compared to healthy brain tissue.[17] Studies of cholinergic innervation of the cerebral cortex and hippocampus and the specific importance of neuronal circuits in those structures have been carried out using a variety of mammal species and a specific combination of antibodies for cholinergic markers such as ChAT and AChE. This has demonstrated that cholinergic innervation is directly related to memory consolidation processes.[5,6,18–20]

Cholinergic markers in the human brain

The human cerebral cortex possesses a complex and extensive network of cholinergic axons[21–23] that innervate or originate in the cholinergic neurons located in the cell nuclei in the NBM (nucleus basalis of Maynert). Both types are immunoreactive to ChAT and AChE enzymes[22,24–26] which absorb stain and present at higher densities in cortical layers III and V.[17] Most of the neurons that are positive for AChE are pyramidal and located in cortical layer V.[17] Immunohistochemical studies performed with the ChAT antibody show a high density of positive fibres and thin cholinergic projections throughout the cerebral cortex.[17] In general, fibres that are immunoreactive to ChAT have a thickened appearance like a string of beads with dotted ends.[27] All cortical areas contain a combination of cholinergic axons that are oriented horizontally, vertically, and transversally to the cortical surface. Horizontal fibres are located in layer I, and to a lesser extent, in layer II. Vertically oriented fibres are located in most layers. Superficial layers (I–III) display dense cholinergic innervations.[22]

The human hippocampus shows immunoreactivity for ChAT and AChE in fimbrial fibres in the subcortical white