SISTEMAS DE NEUROTRANSMISORES EN LINFOCITOS

RESUMEN

Los receptores de neurotransmisores son elementos clave en la comunicación neuronal. Conforman proteínas integrales de membrana especializadas que median respuestas de tipo excitatoria y/o inhibitoria. Estos receptores, junto a enzimas y proteínas que modulan el metabolismo del neurotransmisor, constituyen verdaderos sistemas organizados para una transmisión de la información correcta y eficaz.

Los receptores de neurotransmisores pertenecientes a la familia *Cys-loop*, son canales iónicos activados por ligando. A esta familia pertenecen los receptores nicotínicos de acetilcolina (AChRn), los receptores ionotrópicos de GABA, los receptores de serotonina tipo 3 ($5HT_3$), los receptores de glicina (Gly-R) y los receptores de zinc. Estos receptores también han sido identificados en otros tejidos, por ejemplo epitelio respiratorio, páncreas, endotelio y células inmunes. Existen trabajos que postulan que estos sistemas no-neuronales ejercen una actividad moduladora de procesos celulares tales como diferenciación, migración y proliferación. Sin embargo la función de estos sistemas aún no está completamente esclarecida.

El objetivo de esta tesis es identificar y caracterizar dos sistemas de neurotransmisores en linfocitos humanos: el sistema colinérgico y el sistema GABAérgico.

En primer lugar determinamos la participación del AChRn α7 durante la activación de linfocitos T estimulados con un mitógeno (PHA). Establecimos que durante este proceso aumenta la producción del neurotransmisor ACh, así como también los niveles de ARN mensajero (ARNm) y de proteína del receptor α7.

Además, demostramos que la modulación de dicho receptor por agonistas y antagonistas específicos, inhibe y potencia la proliferación de estas células, respectivamente.

En segundo lugar caracterizamos la presencia de un sistema GABAérgico completo en linfocitos humanos, similar al descripto en neuronas. Determinamos la presencia de enzimas y proteínas que llevan a cabo la síntesis, transporte y catabolismo del neurotransmisor GABA, así como también la presencia y actividad de transportadores de membrana y de receptores ionótropicos de GABA. Al evaluar este sistema durante el proceso de activación, observamos que existe un aumento tanto de los componentes GABAérgicos como de la actividad de los transportadores y receptores, respecto a las células no estimuladas. También observamos que la activación de los receptores por el propio neurotransmisor o por agonistas específicos como muscimol, provoca una disminución de la proliferación inducida por el mitógeno.

Por último, evaluamos la propiedad de plasticidad de estos receptores no neuronales, utilizando como estímulo la exposición a GABA. Se observaron cambios en la expresión del ARNm y en las proteínas de las subunidades de los receptores. Se determinó que durante la exposición al neurotransmisor se activa la vía de Akt. Esta proteína fosforila las subunidades de los receptores de GABA ocasionando una mayor expresión de los mismos en membrana. Estos cambios se corroboraron al detectar un mayor porcentaje de células que responden electrofisiológicamente a la aplicación de GABA.

El trabajo desarrollado en esta tesis aporta nuevos datos acerca de las propiedades y funciones de los sistemas neuronales presentes en linfocitos. Nuestros resultados podrían ser de gran utilidad para el diseño de nuevos tratamientos farmacológicos que actúen sobre estos sistemas, presentando nuevas alternativas en la modulación de la respuesta inmune.

NEUROTRANSMITTER SYSTEMS IN LYMPHOCYTES

SUMMARY

Neurotransmitter receptors are key elements in neuronal communication. They are transmembrane proteins specialized in mediating both excitatory and/or inhibitory responses. These receptors, as well as the enzymes and proteins that are responsible for neurotransmitter metabolism, form organized systems for an efficient and appropriate neuronal transmission.

Neurotransmitter receptors that belong to the *Cys-loop* family are ligand-gated ion channels. Nicotinic acetylcholine receptors (nAChR), ionotropic GABA receptors, serotonin type 3 receptors ($5HT_3$), glycine receptors (Gly-R) and zinc receptors are members of this family. The presence of these receptors has been reported in non-neuronal tissues, such as respiratory epithelium, pancreas, endothelium and immune cells. Previous studies have proposed that these non-neuronal systems are involved in different cellular processes like migration, differentiation and proliferation. However, little is known about their functional role.

The aim of this thesis is to identify and characterize two neurotransmitter systems in human lymphocytes: the cholinergic system and the GABAergic system.

Firstly, we have determined the participation of the α7 nAChR in mitogen (PHA)-induced T cell activation. We have established that ACh synthesis as well as α7 messenger RNA (mRNA) and receptor levels increase during lymphocyte activation. We have also demonstrated that α7 nAChR modulation by specific agonist and antagonist drugs, inhibits and stimulates lymphocyte proliferation, respectively.

Secondly, we have characterized the presence of a complete, neuronal-like GABAergic system in human lymphocytes. We have determined the presence of enzymes and proteins responsible for the synthesis, transport and degradation of the neurotransmitter GABA, and the presence of membrane transporters and ionotropic GABA receptors. We have also observed an increase in these GABAergic elements and in their activity during lymphocyte activation. In addition, we have detected a decrease in mitogen-induced proliferation produced by the activation of ionotropic GABA receptors with GABA and the specific agonist, muscimol.

Finally, we have studied the plasticity of these non-neuronal receptors during GABA exposure. We have detected changes in the mRNA and protein levels of GABA receptor subunits. We have also observed an increase in the activation of the Akt pathway during GABA incubation, which leads to GABA receptor subunit phosphorylation, resulting in a higher receptor expression in the cell membrane. These changes correlate with the detection of a higher number of cells showing electrophysiological activity during GABA exposure.

Findings from these Ph. D. thesis provide new data about the properties and functions of the neurotransmitter systems present in immune cells. Our results could be useful tools for the design of new pharmacological treatments targeting on these systems, to finally introduce alternatives for the modulation of the immune response.

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