RESUMEN

Los fosfolípidos se encuentran a nivel nuclear no sólo en su membrana, sino también en la matriz nuclear y asociados a la cromatina. Estas moléculas tienen una composición y un recambio diferente a las presentes en otras membranas celulares, por lo tanto el núcleo celular constituiría un sitio activo y autónomo respecto al metabolismo de lípidos. Las enzimas relacionadas con la síntesis de lípidos y con la generación de segundos mensajeros lipídicos se han descripto en el núcleo celular aislado, así como también otras proteínas involucradas en los eventos de señalización. Esta señalización intranuclear regularía la expresión de genes actuando de esta manera en los procesos de proliferación, diferenciación y apoptosis celulares. Diversos estudios de nuestro laboratorio demostraron la participación activa del ácido fosfatídico (PA), del diacilglicerol (DAG) y de las enzimas involucradas en sus metabolismos en los procesos de señalización, eventos que se vieron afectados por el envejecimiento, en diferentes áreas del sistema nervioso central.

En este trabajo de Tesis se estudiaron las vías de degradación de PA y su regulación en núcleos aislados de tejido nervioso, empleando como modelo al tejido cerebelar de ratas adultas, y se comparó con núcleos aislados provenientes de un tejido no neural, el tejido hepático. En una primera etapa se demostró la existencia de un metabolismo activo de PA en núcleos de ambos tejidos provenientes de animales adultos al observarse y caracterizarse la actividad enzimática de lípido fosfato fosfatasas (LPPs). Además empleando diferentes moduladores enzimáticos y con el agregado de los sustratos respectivos, se observaron las actividades enzimáticas de diacilglicerol lipasa (DAGL), monoacilglicerol lipasa (MAGL), fosfolipasa A para PA (PA-

PLA), lisofosfatidato fosfohidrolasa (LPAPasa) y de lisofosfatidato fosfolipasa (LPAasa). Se demostró que el PA en el núcleo puede degradarse por dos vías distintas, sin embargo, la vía activa o predominante en cada tejido es diferente. En núcleos de cerebelo la vía principal es la que involucra la acción de LPPs – DAGL; en cambio, en núcleos de tejido hepático el PA es degradado tanto por la vía LPPs – DAGL como por la vía PLA – LPAasa y/o LPAPasa – MAGL.

En una segunda etapa se estudió la regulación de estas enzimas en el núcleo aislado del tejido cerebelar, por agonistas de receptores presentes en esta organela, el ácido retinoico (RA) y el ácido lisofosafatídico (LPA). Se observó que el RA favorece la disponibilidad de DAG y MAG, al inhibir las actividades de DAGL y MAGL, respectivamente; mientras que el LPA disminuye la generación de los mismos al regular negativamente a las LPPs y DAGL.

Por último se evaluó este metabolismo y su regulación por RA en núcleos aislados de cerebelos de ratas seniles que mostró un comportamiento diferente al del adulto. El proceso de envejecimiento favorece una disponibilidad mayor de DAG y de MAG por estímulo de su formación (LPPs y LPAPasa) y por inhibición de su degradación (DAGL y MAGL). Estos cambios relacionados con la edad podrían ser la causa del deterioro neuronal producido en el envejecimiento, o por el contrario, constituir un mecanismo adaptativo frente a los mismos. Además se observó un efecto regulatorio del RA diferente en los núcleos aislados de cerebelos de animales seniles respecto a los del adulto, indicando una función distinta del mismo, dependiendo del estado fisiológico del tejido.

En conclusión, este trabajo de Tesis presenta la primera evidencia de un metabolismo activo de PA a nivel nuclear, donde se encuentran involucradas

actividades enzimáticas diferentes estrechamente relacionadas y las que son moduladas diferencialmente por el envejecimiento y por agonistas de receptores nucleares.

ABSTRACT

The presence of phospholipids in cell nuclei has been observed both at the nuclear envelope and at the nuclear matrix and it has been associated with chromatin. These molecules have a composition and turnover rate different from those of other cellular membranes, thus indicating that the nucleus could be an autonomous active site of lipid metabolism. Enzymes related to lipid synthesis as well as to lipid second messenger generation and proteins involved in signaling events have been found in isolated cellular nuclei. This intranuclear signaling mechanism seems to be involved in the regulation of gene expression, thus modulating proliferation, differentiation and apoptosis processes. Findings from our laboratory have demonstrated that phosphatidic acid (PA), diacylglycerol (DAG) and enzymes related to their metabolism, all found to be affected by ageing, have an active role in different areas of the central nervous system. In view of this, the purpose of this Ph. D. thesis work was to study PA metabolism pathways and their regulation in isolated nuclei from neural tissue using rat cerebellar tissue as a model, and to compare them with those in isolated nuclei from non-neural tissue, rat liver tissue.

To this end, the enzymatic activity of lipid phosphate phosphatases (LPPs) was firstly characterized, which demonstrated an active PA metabolism in nuclei from both adult animal´s tissues. Furthermore, using different enzymatic modulators as well as the substrates corresponding to each enzyme, it was possible to observe diacylglycerol lipase (DAGL), monoacylglycerol lipase (MAGL), PA-selective phospholipase A (PA-PLA), lysophosphatidic phosphohydrolase (LPAPase) and lysophosphatidic phospholipase (LPAase) activities. It was thus shown that PA in isolated nuclei is metabolized by two

different pathways in spite of the fact that the active or predominant pathway is different for each tissue. It was also shown that in rat cerebellar nuclei LPPs-DAGL action is the main pathway involved in PA degradation whereas in rat liver nuclei PA is metabolized not only by LPPs-DAGL pathway but also by PLA-LPAase and/or LPAPase-MAGL ones.

The second stage of this study was focused on studying the regulation of these enzymes by nuclear receptor agonists, retinoic acid (RA) and lysophosphatidic acid (LPA). It was observed that RA increases the availability of DAG and MAG by inhibiting DAGL and MAGL activities, respectively while LPA diminishes their formation by the negative modulation of LPPs and DAGL activities.

The third stage of this study was focused on evaluating this metabolism and its regulation by RA in cerebellar nuclei from aged rats that were found to be different from the adult ones. Ageing promotes an increase in the availability of DAG and MAG due to an increase in their synthesis (LPPs and LPAPase) and an inhibition of their degradation (DAGL and MAGL). These aged-related changes could be either the cause of neuronal decline as a result of ageing or an adaptive mechanism in response to the changes produced during this process. A different RA effect was also observed in aged nuclei with respect to adult ones, thus indicating a distinct RA role that depends on the tissue physiological state.

Summing up, this thesis work provides the first lines of evidence of an active PA metabolism in nuclei in which different enzymatic tightly related activities, which are modulated by ageing and nuclear receptor agonists, are involved.

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