RESUMEN

En este trabajo de Tesis se investigaron los efectos de la hormona paratiroidea (PTH) en enterocitos de duodeno de ratas jóvenes (3 meses) y seniles (24 meses) y de adenosina trifosfato (ATP) en células Caco-2 derivadas de adenocarcinoma de colon, sobre las cascadas de señalización de las MAP quinasas (MAPKs) y su participación en la proliferación de estas células. Los resultados demuestran que PTH estimula, en forma rápida y transitoria, igual que a ERK1/2 (estudios previos), la fosforilación y actividad de JNK1/2 en células intestinales de ratas jóvenes, siendo los efectos de la hormona dependientes del Ca^{2+} intra y extracelular. Con el envejecimiento los efectos de PTH sobre JNK1/2 disminuyen significativamente. La expresión proteica basal de JNK1/2 no difiere entre enterocitos de ratas jóvenes y seniles, no obstante su fosforilación basal es mucho más elevada en células intestinales de seniles explicando la menor activación de JNK1/2 en respuesta a la hormona con el envejecimiento. PTH no modifica ni la actividad ni la fosforilación basal de p38 MAPK en enterocitos de ratas jóvenes. Sin embargo, en seniles indujo la fosforilación de esta quinasa de manera dependiente del tiempo, siendo máxima a los 5 minutos de tratamiento. PTH incrementa la síntesis de ADN, siendo mayor la magnitud en enterocitos de ratas jóvenes (+30%) que en seniles (+18%). ERK1/2 y JNK1/2 participan en el efecto proliferativo de la hormona en enterocitos de ratas jóvenes. En seniles, además de estas dos vías, también participa p38 MAPK. En la línea celular Caco-2, el ATP induce la rápida fosforilación de ERK1/2, p46 JNK y p38 MAPK. Una vez activadas, ERK1/2 y JNK translocan al núcleo. La estimulación de las quinasas también

se observó en presencia de UTP, UDP y ATPγS sugiriendo la participación de los subtipos de receptores $P2Y_2$, $P2Y_4$, $P2Y_6$ y probablemente $P2Y_{11}$ en la activación purinérgica. Estudios de RT-PCR y la secuenciación de sus productos confirmaron la expresión de $P2Y_2$ y $P2Y_4$ en estas células. Se comprobó que el ATP aumenta la concentración de Ca^{2+} intracelular y, que en el mecanismo de activación de las MAPKs participan el Ca^{2+}, Src, y en menor grado las vías AMPc/ PKA y PKC, y la transactivación del receptor del factor de crecimiento epidermal (EGFR). La activación de las MAPKs por ATP en las células Caco-2, contribuye a la fosforilación de los factores de transcripción ATF-1, ATF-2 y JunD e induce la expresión de c-Fos y miembros de la familia de Jun. Además las MAPKs participan en la inducción y en la fosforilación de la fosfatasa dual MKP-1, capaz de inactivar a ERK1/2, JNK1/2 y p38 MAPK mediante la desfosforilación de dos residuos críticos en el "*loop"* de activación. Finalmente, el ATP a través de las cascadas de señalización de las MAPKs estimula la proliferación (+27%) de las células Caco-2.

En conjunto, estos estudios son aportes originales al conocimiento de los mecanismos de acción de PTH y ATP en células intestinales. La comprensión del deterioro de las funciones de PTH con el envejecimiento, y de las modificaciones inducidas por el ATP en células tumorales, nos permiten ampliar las bases moleculares de la regulación de la fisiología intestinal.

ABSTRACT

In the present study, we investigated the effects of parathyroid hormone (PTH) on duodenal enterocytes from young (3 months) and aged rats (24 months), and the role of adenosine triphosphate (ATP) on Caco-2 cells derived from colon adenocarcioma, on MAP kinases signaling cascades (MAPKs) and their involvement in cell proliferation. Our results show that, in intestinal cells from young rats, PTH induces a transient and rapid increment, as happens with ERK1/2 (previous studies), in JNK1/2 phosphorylation and activity, effects that depend on intra and extracellular calcium. PTH actions on JNK1/2 are significantly diminished with ageing. JNK1/2 basal protein expression is not different in the enterocytes from young and aged rats, however basal protein phosphorylation increases with ageing explaining the lower JNK1/2 activation in response to PTH in aged rats. The hormone does not change the basal phosphorylation and activity of p38 MAPK in young enterocytes. However, in cells from aged rats, it induced the phosphorylation of p38 MAPK in a time dependent manner, peaking at 5 min. PTH increased intestinal cells DNA synthesis, being the effect on young enterocytes (+30%) more pronounced than in aged ones (+18%). ERK1/2 and JNK1/2 participate in the proliferative role of the hormone in duodenal cells from young rats. In aged enterocytes, besides these two pathways, p38 MAPK is also involved. ATP induces the rapid phosphorylation of ERK1/2, p46 JNK and p38 MAPK in Caco-2 cells, which is followed by traslocation of active ERK1/2 and JNK into the nucleous. UTP, UDP and ATPγS induce MAPKs phosphorylation, suggesting the involvement of $P2Y_2$, $P2Y_4$, $P2Y_6$ and probably $P2Y_{11}$ subtypes receptors in purinergic actions.

RT-PCR studies and PCR product sequencing supported the expression of $P2Y_2$ and $P2Y_4$ in this cell line. ATP increases the intracellular calcium concentration. In addition ATP-induced phosphorylation of MAPKs in Caco-2 cells was dependent on calcium influx and intracellular calcium release, Src and partially dependent on the cAMP/PKA and PKC pathways and EGFR transactivation. MAPKs activation by ATP is involved in ATF-1, ATF-2 and JunD transcription factors phosphorylation and in c-Fos and Jun family members induction. Moreover, MAPKs participate in the induction and phosphorylation of the dual MKP-1 phosphatase, capable of inactivating ERK1/2, JNK1/2 and p38 MAPK through the dephosphorylation of two critical residues in the activation loop. Finally, ATP through MAPKs signaling cascades stimulates the proliferation (+27%) of Caco-2 cells.

In summary, these studies are originals contributions to the knowledge of PTH and ATP mechanisms actions on intestinal cells. The comprehension of PTH functions deterioration with ageing, and of the modifications induced by ATP on tumoral cells, let us amplified the molecular bases of the regulation of intestinal physiology.

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Publicaciones originadas de esta Tesis