

Enhancing Effect of Flavonoids on Transport of Ginkgolide K Across an hCMEC/D3 Cell Monolayer as a Blood-Brain Barrier Model

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SUMMARY. The transports of ginkgolides across blood brain barrier (BBB) are critical to their neuroprotective effects. Thus, the improved transport of ginkgolide through BBB is considered as a rational approach for the treatment of cerebral ischemia. In this report, we investigated the effect of flavones (luteolin, apigenin, chrysin and hesperidin) and flavonols (kaempferol, quercetin, morin and myricetin) on the transports of ginkgolide K (GK) across the hCMEC/D3 cell monolayer (a model of BBB *in vitro*). Cell to medium ratio of GK content, GK transport improved by flavonoids, the apparent permeability coefficients (P_{app}) and the efflux ratio were investigated in the Transwells by ULPC-ELSD in an attempt to describe the transport characteristic of GK. The efflux ratios of GK were significantly decreased in a dosage-dependent manner along with enhancement of flavonoid concentrations with an exception of rutin and hesperetin. The number and localization of hydroxyl groups on flavonoid backbone played a vital role in regulating the transport of GK across monolayer cells. The glycosylation of the C(3) or A(7) hydroxyl group of flavonoid led to the loss of activity and no inhibitory effects. Additionally, flavonoids and cyclosporin A (Cyc A) were all the inhibitors of P-glycoprotein (P-gp) and their relationship belonged to the synergistic effect. The findings provided important information for illuminating the enhancing transport of ginkgolide across BBB through mediation of P-gp controlled by some flavonoids.

RESUMEN. El transporte de ginkgólidos a través de la barrera hematoencefálica (BBB) es crítico para sus efectos neuroprotectores. Por lo tanto, el transporte mejorado del ginkgólido a través de BBB se considera como un enfoque racional para el tratamiento de la isquemia cerebral. En este informe, investigamos el efecto de las flavonas (luteolina, apigenina, crisina y hesperidina) y los flavonoles (kaempferol, quercetina, morina y myricetina) en los transportes de ginkgólido K (GK) a través de la monocapa de células hCMEC/D3 (un modelo de BBB *in vitro*). La relación célula a medio del contenido de GK, el transporte de GK mejorado por los flavonoides, los coeficientes de permeabilidad aparente (P_{app}) y la relación de flujo de salida fueron investigados en los Transwell por ULPC-ELSD en un intento por describir la característica de transporte de GK. Las proporciones de flujo de salida de GK disminuyeron significativamente de una manera dependiente de la dosis junto con el aumento de las concentraciones de flavonoides con excepción de rutina y hesperetina. El número y la localización de los grupos hidroxilo en la columna vertebral de los flavonoides desempeñaron un papel vital en la regulación del transporte de GK a través de las células de la monocapa. La glicosilación del grupo hidroxilo C(3) o A(7) del flavonoide condujo a la pérdida de actividad y a efectos no inhibitorios. Además, los flavonoides y la ciclosporina A (Cyc A) fueron todos inhibidores de la P-glicoproteína (P-gp) y su relación es parte del efecto sinérgico. Los hallazgos proporcionaron información importante para aclarar la mejora del transporte de ginkgólidos a través de BBB mediante la mediación de P-gp controlada por algunos flavonoides.

KEY WORDS: BBB, flavonoid, ginkgolide K, transport.

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