行政院國家科學委員會專題研究計畫　成果報告

Carnitine transporters 對懷孕期間藥物吸收及分佈的影響

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報告類別：研究報告-精簡報告

Purpose. To examine the inhibitory effect of anticonvulsants on carnitine transport by the human placental carnitine transporter.

Methods. Uptake of radiolabeled carnitine by human placental brush-border membrane vesicles was measured in the absence and presence of tiagabine, vigabatrin, gabapentin, topiramate, valproic acid, and phenytoin. The mechanism of the inhibitory action of tiagabine was determined.

Results. Most of the anticonvulsants inhibited placental carnitine transport. Kinetic analyses showed that tiagabine had the greatest inhibitory effect (IC50 190 μM) and the order of inhibitory potency was tiagabine > phenytoin > gabapentin > valproic acid > vigabatrin, topiramate > lamotrigine. Further studies showed that tiagabine competitively inhibited carnitine uptake by the human placental carnitine transporter, suggesting it may be a substrate for this carrier.

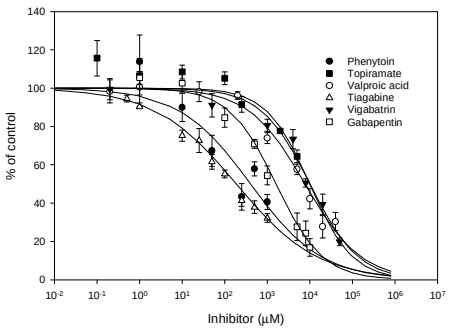

Figure. Dose-response study of carnitine uptake in the presence of tiagabine (0.5-1,000 μM), phenytoin (1-1,000 μM), gabapentin (1-10,000 μM), valproic acid (0.2-40,000 μM), topiramate (0.1-5,000 μM), or vigabatrin (0.2-50,000 μM). The data are presented as the mean±SE for 3-5 experiments, each in triplicate.

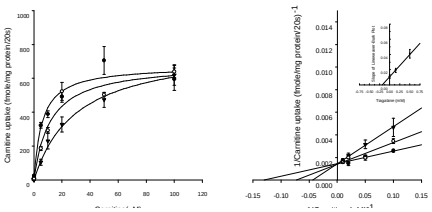

Figure. Concentration-dependent carnitine uptake (0.05 μM to 100 μM) in the presence of tiagabine at a concentration of 0 mM (filled circles), 0.15 mM (empty circles), or 0.5 mM (filled triangles). **A**. Nonlinear regression analysis of carnitine uptake. **B**. Lineweaver-Burk plot analysis of carnitine uptake. In the insert, a value of about 193 μM was estimated for the inhibition constant (Ki) for tiagabine from the intercept on the x axis. The data are presented as the mean±SE for three experiments, each in

triplicate. Each plot was generated from the mean of the individually fitted parameters.

Table. Inhibition of carnitine uptake by anticonvulsants and other compounds in BBMV isolated from human placenta. The 20 sec uptake was initiated by mixing 60 µl of uptake buffer containing 80 nM ^{3}H-carnitine and inhibitors with 40 µl of vesicle suspension. The data are presented as the mean±SD for at least three experiments in triplicate.

Inhibitors	Relative uptake (% control)		IC50 (mM)
	1 mM	0.1 mM	
Control	100	100	-----
Carnitine	2.70±4.17 *	32.0±11.0*	-----
Tiagabine	31.6±6.60 *	51.6±7.64*	0.19±0.05
Phenytoin	39.0±6.32 *	75.1±2.39*	0.40±0.09
Gabapentin	57.0±3.87 *	84.6±9.88*	1.60±0.83
Valproic acid	68.3±2.40 *	85.3±2.90*	7.70±3.69
Topiramate	66.4±9.30 *	91.7±10.4	9.91±2.61
Vigabatrin	62.6±5.66 *	83.0±3.66*	10.0±2.84
Lamotrigine	-----	94.5±12.7	-----

* Significantly different from the control uptake by Student's t test ($p<0.05$)

Conclusions. Although the involvement of carnitine deficiency in fetal anticonvulsant syndrome requires further evaluation, potential interference with placental carnitine transport by several anticonvulsants was demonstrated. Despite the higher inhibitory potency of tiagabine, given the therapeutic unbound concentrations, the results for valproic acid and phenytoin are probably more clinically significant.