Influence of Cilnidipine on Catecholamine Release Evoked by Cholinergic Stimulation and Membrane Depolarization in the Perfused Rat Adrenal Gland

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Cilnidipine (FRC-8635) is a newly synthesized novel DHP type of organic Ca^{2+} channel blockers that have been developed so far in Japan (Yoshimoto et al., 1991; Hosono et al., 1992). It also has a blocking action on L-type voltage-dependent Ca^{2+} channel (VDCCs) in the rabbit basilar artery (Oike et al., 1990) and a slow-onset and long-lasting hypotensive action in clinical and experimental studies (Ikeda et al., 1992; Tominaga et al., 1997). Recent electrophysiological data indicate that cilnidipine might be a dual-channel antagonist for peripheral neuronal N-type and vascular L-type Ca^{2+} channels (Oike et al., 1990; Fujii et al., 1997; Uneyama et al., 1997). However, little is known about the involvement of N-type VDCCs in contributing to the muscarinic receptor-mediated CA secretion. Therefore, the present study was attempted to investigate the effect of cilnidipine on secretion of catecholamines (CA) evoked by ACh, high K^+, DMPP and McN-A-343 from the isolated perfused rat adrenal gland. Cilnidipine (1-10 μM) perfused into an adrenal vein for 60 min produced dose- and time-dependent inhibition in CA secretory responses evoked by ACh (5.32 x 10^{-3} M), DMPP (10^{-4} M for 2 min) and McN-A-343 (10^{-4} M for 2 min). However, lower dose of lobeline did not affect CA secretion by high K^+ (5.6 x 10^{-2} M), higher dose of it reduced greatly CA secretion of high K^+. Cilnidipine itself did also fail to affect basal catecholamine output. Furthermore, in adrenal glands loaded with cilnidipine (10 μM), CA secretory response evoked by Bay-K-8644 (10 μM), an activator of L-type Ca^{2+} channels was markedly inhibited while CA secretion by cyclopiazonic acid (10 μM), an inhibitor of cytoplasmic Ca^{2+}-ATPase was no affected. Moreover, ω-conotoxin GVIA (1 μM), given into the adrenal gland for 60 min, also inhibited time-dependently CA secretory responses evoked by ACh and high K^+.

Taken together, these results obtained from the present study suggest that cilnidipine inhibits greatly CA secretion evoked by stimulation of cholinergic (both nicotinic and muscarinic) receptors from the isolated perfused rat adrenal gland without affecting the basal release. However, at lower dose, cilnidipine did not affect that by membrane depolarization while at larger dose inhibited that. It seems likely that this inhibitory effect of cilnidipine is exerted by blocking both L- and N-type VDCCs on the rat adrenomedullary chromaffin cells. It is sggested that there is similarity in the mode of action between cilnidipine and ω-conotoxin GVIA in rat adrenomedullary CA secretion.