Cloned human TACE cDNA was expressed in baculovirus-insect cells and purified to homogeneity for screening TACE inhibitors. Established fluorogenic assay with recombinant human TACE enzyme in the format of 96-well plate is easily adapted for high throughput screening. This HTS system is robustly applicable to the discovery of TACE inhibitor owing to its high sensitivity, precision, accuracy, and stability.

[PA1-3] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

INFLUENCE OF CILNIDIPINE ON RELEASE OF NOREPINEPHRINE AND EPINEPHRINE EVOKED BY CHOLINERGIC STIMULATION FROM THE RAT ADRENAL MEDULLA

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Adrenal medullary chromaffin cells secrete catecholamines in response to nicotinic agonists (Douglas & Rubin, 1961; Wakade, 1981; Amy & Kirshner, 1982). Several types of voltage-dependent Ca2+ channels are present on adrenal chromaffin cells, but the role of each type in the catecholamine secretion process remains controversial. Adrenal catecholamine secretion is also mediated by muscarinic receptors in various species (Douglas & Poisner, 1965; Harish et al. 1987; Nakazato et al. 1988; Kimura et al. 1992). Also, little is known about the involvement of N-type voltage-dependent Ca2+ channels in the muscarinic receptor-mediated secretion of catecholamines (Uceda et al. 1994). The present study was designed to investigate the effects of L- and N-type voltage-dependent Ca2+ channel blocker, cilnidipine on the secretion of epinephrine (EP) and norepinephrine (NE) from the isolated perfused rat adrenal gland in response to acetylcholine, the nicotinic agonist DMPP and the muscarinic agonist McN-A-343 to elucidate the functional role of voltage-dependent Ca2+ channels in controlling the adrenal secretion of EP and NE. Acetylcholine (ACh, 5.32 mM), high K+ (56 mM), DMPP (100 μM for 2 min), McN-A-343 (100 μM for 2 min), cyclopiazonic acid (10 μM for 4 min) and Bay-K-8644 (10 μM for 4 min) evoked a 1.3 ~ 5.3-fold greater secretion of EP than NE in the perfused rat adrenal gland. The perfusion of cilnidipine (1 ~ 10 μM) into an adrenal vein for 20 min produced relatively dose-dependent inhibition in secretion of EP and NE evoked by ACh, high K+, DMPP, and McN-A-343. Moreover, under the presence of cilnidipine (1 ~ 10 μM), releasing responses of EP and NE evoked by cyclopiazonic acid and Bay-K-8644 were also greatly reduced. Taken together, these results suggest that cholinergic stimulation and membrane depolarization enhance more release of EP than NE in the perfused rat adrenal medulla, and that cilnidipine inhibits the release of EP and NE evoked by stimulation of cholinergic receptors as well as by membrane depolarization. It seems that this inhibitory effect of cilnidipine is associated with the inhibition of calcium influx through the blockade of both L- and N-type calcium channels located in the rat adrenomedullary chromaffin cells.

[PA1-4] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

An antiarrhythmic drug for atrial fibrillation from Chelidonium majus

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The therapeutic potential of currently available antiarrhythmic drugs is limited by their tendency to induce proarrhythmic and extracardiac side effects. An ideal antiarrhythmic agent would selectively prolong the action potential duration more in extraordinarily depolarized cardiac myocytes than in normal cells, and show tissue selectivity. Voltage-gated K+ (Kv) channels