[PA1-1] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Bone formation-suppressing Activities in Osteoblast like-UMR106 cells by high Glucose contents

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Diabetes is complex in nature but it gets further complicated in associating with number of other diseases like hypertension, ratinal disintegration, renal failure and many others. The latest addition to diabetic-complication is its association with bone degeneration disease; osteoporosis, which is a form of bone loss. In both the types of primary diabetes, the insulin dependent diabetes millitus (IDDM) as well in insulin independent diabetes millitus (IIDM) the glucose metabolism is altered. And especially in IDDM, glucose concentration has been observed to be too high. An altered extra cellular glucose, effect significantly the cellular processes; like modulation of cellular redox, dysfunction in cellular metabolic paths and glycosylation of proteins and DNA thus affecting cell growth and function. It may be possible that such situation may be in the bone forming cells too, hence a possible link between high glucose contents and origin of osteoporosis may exist. To prove such linkage in this study, the effect of different concentration of glucose were observed in osteoblast-like UMR106 cells. And the effects of elevated glucose concentrations (22mM, 33mM) were found to have inhibitory in nature on bone formation activities like measurements of alkaline phosphatase and collagen synthesis. Such inhibition in case of alkaline phosphatase activity was recorded at both concentrations, where degree of inhibition also increased with prolongation of duration days. Similar observation was also recorded with collagen synthesis. Such inhibitory activities of glucose is seems to be very specific to its nature only, as other derivative like mannitol failed to produced such inhibition, thus discarding the osmotic theory action. Utilization of glucose such inhibitory action also proved by reduction in glucose contents in protein assay.
This study clearly shows that high glucose contents have suppressing effect in bone formation activities, which may participate in the cause of osteoporosis also.

[PA1-2] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

High Throughput Fluorogenic Assay for TNF-alpha Converting Enzyme(TACE) inhibitors

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Human tumor necrosis factor-alpha (TNFa) is a key pro-inflammatory cytokine produced by activated monocytes and macrophage as a part of the self-defence machinery. TNF-a converting enzyme (TACE) is the metalloproteinase that processes the membrane bound precursor of TNFa to the soluble component. Recently, several evidences demonstrate that selective inhibition of TACE could be a potential strategy for modulating inflammatory response in many diseases such as rheumatoid arthritis, Crohn's disease and inflammatory bowel disease.

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