FS8-1

Discovery of a novel compound, KR62980 with anti-osteoporotic activities acting on both osteoblasts and osteoclasts

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Osteoporosis is the most common metabolic bone disorder and remains an increasingly significant problem in domestic as well as worldwide circumstance. Bone homeostasis is maintained by a balance between bone resorption by osteoclasts and bone formation by osteoblasts, and a balance shift for an excess of resorption over formation leads to the bone loss and increased propensity to fracture that is characteristic of osteoporosis. We discovered KR62980 with novel structure initially identified from high throughput screening of Korea Chemical Bank, followed by optimization process. KR62980 stimulated differentiation of preosteoblasts as well as bone marrow stromal cells to osteoblasts, accompanied by increased alkaline phosphatase, Runx-2, and BMP expression. The in vivo bone formation effects by KR62980 were confirmed by mouse calvaria implantation model. In addition, KR62980 inhibited osteoclast differentiation and formation of resorption pit concurrent with NF-B inactivation. The in vivo anti-resorptive activity of KR62980 was observed by LPS-induced resorption model and ovariectomy model. Taken together, these results suggest that KR62980 has dual beneficial effects on osteoporosis treatment, namely osteoblast stimulation and osteoclast inhibition. Based on the present study, KR-62980 may have great potential for the development of novel anti-osteoporotic agents.

FS8-2

Discovery & development of Schizophrenia drug (YKP1358)

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YKP1358 is a novel "atypical" antipsychotic drug with selective 5-hydroxytryptamine2/dopamine2 receptor binding profiles and antagonist activity. In behavioral studies, YKP1358 antagonizes apomorphine-induced climbing behavior and 5-hydroxytryptamine induced head twitches in mice. In conditioned avoidance paradigm in rats, YKP1358 inhibits the avoidance response ; however, unlike other antipsychotic drugs, catalepsy is only observed at much higher doses. These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. On the basis of these result, it would be predicted that YKP1358 will have an atypical profile and will be less undesirable extrapyramidal symptom and weight gain than currently available drugs.

FS8-3

Discovery of KR-33028, a novel Na+/H+ exchanger isoform-1 (NHE-1) inhibitor as a cardioprotective agent

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Since the excessive activation of Na+/H+ exchanger isoform-1 (NHE-1) has been known to play an important role in the progression of ischemia/reperfusion injury, many efforts have been devoted to develop a potent and selective NHE-1 inhibitor as cardioprotective drug. From our efforts to find a novel NHE-1 inhibitor based on bicyclic template, we found that (benzo[b]thiophene-2-carbonyl) guanidines with 4-substituent including halogen, nitrile, nitro, alkyl, and aryl groups showed good NHE-1 inhibitory activity which was well translated into the cardioprotective efficacy. In isolated rat ischemic heart model, the 4-cyano compound (KR-33028) significantly improved the recovery of cardiac contractile function(63% LVDP), diminished the contracture(20 mmHg LVEDP), and reduced the damage of myocyte(13 IU/g LDH), compared with the vehicle group(13% LVDP, 55 mmHg LVEDP, and 28 IU/g LDH). In addition, KR-33028 excellently limited the infarct size in the in vivo myocardial infarction rat(38% IS/AAR vs 59% of vehicle) and beagle dog model. Furthermore, KR-33028 showed a good pharmacokinetic and safety profile. This study suggests the possibility that KR-33028 can be developed as a cardioprotective agent against ischemia/reperfusion injury.

FS8-4

Development of VR1 antagonists

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Although the presence of capsaicin (CAP) receptor and its functional role in the pain sensory system are now known, an endogenous activator of the receptor has not yet been found. Previously, we found that products of lipoxygenases (LO) directly activate the CAP receptor in isolated membrane patches of sensory neurons. Among LO products, 12-hydroperoxytetraenoic acid (12-HPETE) activates single-channel currents most potently. Products of LOs other than 12-HPETE also activated the CAP channels. Because CAP and 12-HPETE act on the capsaicin receptor, the two molecules share a structural similarity. Indeed, 3D structurs of CAP fits well to the S-shaped 12-HPETE. We further studied the upstream signals of the LO/VR1 signaling pathways and concluded that bradykinin, a pain causing substance excites sensory neurons via PLA2/LO/VR1 pathway. Since these results suggest that VR1 play an important role in mediating inflammatory pain, we tried to develop VR1 antagonists as novel analgesics. In the present seminar, we present piece of evidence that VR1 antagonists would be used as novel analgesics in clinics in future. [Supported by National Creative Initiatives Program of Korea]