and decreased the plasma glucose levels and FFA in HF diet-induced obesity of C57BL/6 mice.

[PA1-10] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Metabolism of YH3945, a novel anticancer drug, in rats using 14C-labeled compound

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The metabolism of a novel anticancer agent 1-{3-[3-(4-Cyano -benzyl)-3H-imidazol-4-yl]-propyl}-3-(6-methoxy-pyridin-3-yl)-1-(2-trifluoromethyl-benzyl)-thiourea (YH3945) were investigated in the Sprague-Dawley rat after single oral and i.v. administration of [14C]-YH3945. Bile, feces, urine and plasma were collected and analyzed by an HPLC system equipped with multiple detectors. The present analysis system includes the simultaneous detection technique of three different detectors (diod array detector-radioactivity flow detector-tandem mass spectrometry) in single run. The structures of each metabolite were characterized based on UV, tandem mass (MS2 and MS3) and NMR (1H and TOCSY) spectral analyses. YH3945 was metabolized to seventeen different metabolites including glucuronide conjugate. The four major metabolic pathways of YH3945 in rat were identified as O-demethylation of pyridine moiety, N-debenzylation of imidazol moiety, hydroxylation of aromatic ring and recyclization between pyridine and benzylic carbon. Especially, nonenzymatic reaction mechanism of metabolite generated by the recyclization was theoretically postulated.

[PA1-11] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]

Attenuation of nicotine-induced locomotor sensitization in μ-opioid receptor knockout mice

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The present study was undertaken to examine the hypothesis that μ-opioid receptors play a crucial role in behavioral sensitization to nicotine using μ-opioid receptor knockout mice.
All mice were treated acutely or repeatedly with nicotine 0.05 mg/kg twice daily for 7 consecutive days. The mice were challenged with nicotine on day 11. And locomotor activity was measured for 30min. Locomotor activity challenged by acute nicotine was no difference between μ-opioid receptor knockout and wild-type mice. Repeated treatment with nicotine induced behavioral sensitization in wild-type mice on days 7 and 11. In contrast, nicotine exposure failed to develop behavioral sensitization in μ-opioid knockout mice. This behavioral sensitization was accompanied by an incerese in D(2) receptor binding in striatum of the μ-opioid knockout mice compared with the wild-type mice on day 7. However, D(1) receptor expression was not changed in the striatum and nucleus accumbens.
These results suggest that abolishment of nicotine-induced behavioral sensitization in the μ-opioid receptor knockout mice may be related to the increase of D(2) receptor binding in the striatum.

[PA1-12] [04/17/2003 (Thr) 14:00 - 17:00 / Hall P]