5

Dopamine D_2 Receptor Occupancy in Normal Humans Treated with a Novel Antipsychotic Drug YKP1358 Measured by PET and [11C]Raclopride

Departments of Nuclear Medicine[1], Neuropsychiatry[2], and Pharmacology[3]

JS Lee[1] *, SJ Kim[1], KJ Lee[2], E Kim[2],K-S Yu[3], I-J Jang[3], JS Kwon[2], WJ Kang[1], JM Jeong[1], DS Lee[1], J-K Chung[1], MC Lee[1]

Purpose: YKP1358 is a novel serotonin ($5\text{-}HT_{2A}$) and dopamine (D_2) antagonist, and fitted the general profile of an atypical neuroleptic agent in preclinical studies. The time course of D_2 receptor occupancy in the brain of living human after a single oral dose of YKP1358 was measured using PET and related to the plasma drug levels. **Methods:** A single oral dose, dose escalation (100 mg, 200 mg, and 250 mg), open-label study was performed in 9 healthy male volunteers (3 per each dose) using the [^{11}C]raclopride PET. After the baseline scan, each subject was studied at 2, 5, and 10 hours after the single administration of YKP1358. Blood samples for evaluation of plasma concentration of YKP1358 were also taken at various time points (0-32 hours post-dose). Binding potential (BP) of [^{11}C]raclopride in the putamen was estimated with simplified reference tissue model and percent reduction of the BP was calculated to obtain the D_2 receptor occupancy. BP parametric image was generated using a pixel-wise Logan noninvasive plot. **Results:** T_{max} of plasma concentration-time profiles was 0.67 hours, and elimination half-life was 5.71, 7.46, and 8.58 hours in 100 mg, 200 mg, and 250 mg dosing groups, respectively. D_2 receptor occupancy of YKP1358 was 60 to 80% at 2 hours, 40 to 60% at 5 hours, and 20 to 50% at 10 hours. The relationship of plasma concentration and D_2 receptor occupancy of YKP1358 was well predicted by Emax model, and Emax was 100 %, EC50 was 8.9 (±1.1) ng/ml, and Hills coefficient was 0.525. **Conclusion:** PK profile of YKP1358 showed individual variation, but the D_2 receptor occupancy was less variable and well predicted by an Emax model. Since D_2 antagonists show therapeutic effects at 50 to 80% D_2 occupancy and the EC50 of YKP1358 is less than 10 ng/ml, doses of YKP1358 which maintain plasma concentrations above 10 ng/ml are expected to show therapeutic effects.

6

Dopamine Release in Human Striatum Induced by Repetitive Transcranial Magnetic Stimulation over Dorsolateral Prefrontal Cortex

Department of Nuclear Medicine, Seoul National University College of Medicine

Sang Soo Cho *, Eun Jin Yoon, Yu Kyeong Kim, Won Woo Lee, Sang Eun Kim

Purpose: Animal study suggests that prefrontal cortex plays an important Animal studies suggest that prefrontal cortex plays an important role in the modulation of dopamine (DA) release in subcortical areas. However, little is known about the relationship between DA release and prefrontal activation in human. We investigated whether repetitive transcranial magnetic stimulation (rTMS) over left dorsolateral prefrontal cortex (DLPFC) influences DA release in human striatum with SPECT measurements of striatal binding of [123I]iodobenzamide (IBZM), a DA D2 receptor radioligand that is sensitive to endogenous DA. **Methods:** Five healthy male volunteers (age, 25±2 yr) were studied with brain [123I]IBZM SPECT under three conditions (resting, sham stimulation, and active rTMS over left DLPFC), while receiving a bolus plus constant infusion of [123I]IBZM. DLPFC was defined as a 6 cm anterior and 1cm lateral from the primary motor cortex. rTMS session consisted of three blocks, in each block, 15 trains of 2 sec duration were delivered with 10 Hz stimulation frequency, 100% motor threshold, and between-train intervals of 10 sec. Striatal V3", calculated as (striatal - occipital)/occipital activity ratio, was measured under equilibrium condition, at baseline and after sham and active rTMS. **Results:** Sham stimulation did not affect striatal V3". rTMS over DLPFC induced reduction of V3" in the ipsilateral and contralateral striatum by 9.7% ± 1.3% and 10.6% ± 3.2%, respectively, compared with sham procedures ($P < 0.01$ and $P < 0.01$, respectively), indicating striatal DA release elicited by rTMS over DLPFC. V3" reduction in the ipsilateral caudate nucleus was greater than that in the contralateral caudate nucleus (9.9% ± 4.5% vs. 6.6% ±3.1%, $P < 0.05$). **Conclusion:** These data demonstrate DA release in human striatum induced by rTMS over DLPFC, supporting that cortico-striatal fibers originating in prefrontal cortex are involved in local DA release.