PW01-27 - **TRANSLATIONAL PHARMACOLOGY OF QUETIAPINE AND NORQUETIAPINE: PRECLINICAL FINDINGS SUPPORT MULTIFUNCTIONAL PSYCHOTROPIC PROPERTIES**

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Objectives: Clinical studies demonstrate that quetiapine is efficacious in schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and generalized anxiety disorder. The pharmacological basis for this broad range of clinical effects is not completely understood. The current experiments evaluated pharmacological assays investigating the receptor-binding characteristics of quetiapine and norquetiapine (the major human metabolite) and compared these with other atypical antipsychotics and standard antidepressants.

Methods: In vitro receptor-binding assays utilized cloned human targets including norepinephrine transporter (NET), dopamine D2 receptor, and serotonin 5-HT1A, 5-HT2A, and 5-HT2C receptors stably expressed in CHO or HEK cell lines. In vitro functional studies included uptake-inhibition assays for NET and GTPgammaS assays for D2/D3 antagonist and 5-HT1A agonist activity.

Results: Norquetiapine demonstrated high affinity at 5-HT2A receptors (5 nM) and moderate/high affinity at NET (29 nM) and 5-HT2C receptors (76 nM), while quetiapine had moderate affinity at 5-HT2A receptors (29 nM), weak affinity at 5-HT2C receptors (2800 nM), and lacked appreciable affinity at NET. Both quetiapine and norquetiapine showed moderate affinity at D2 receptors (56 nM and 59 nM, respectively) with moderate/low-potency antagonist activity. Both quetiapine and norquetiapine exhibited low affinity at 5-HT1A receptors (1800 nM and 570 nM, respectively) with low-potency agonist activity.

Conclusions: These experiments confirm that quetiapine-norquetiapine have multiple pharmacological effects at targets associated with psychotropic drug action. This combination of effects by quetiapine-norquetiapine at dopaminergic, serotonergic, and noradrenergic targets may explain the antipsychotic, antidepressant, and anxiolytic properties of quetiapine.

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