Antidepressant Drug Evaluation Using in vivo Screening Tool

Hanju Yi*, Hyunsik Nam, Yujin Shin

SK Bio-Pharmaceuticals, SK Corporation, 140-1 Wonchon-dong, Yuseong-gu, Daejeon, 305-712, Korea

Since monoamine oxidase inhibitors originally developed for anti-tuberculosis treatments were used as antidepressants in the late 1950s, novel antidepressants with various targets have been emerged. The application of tricyclics such as imipramine for depression treatment led to the period of monoamine reuptake inhibitors represented by SSRIs (serotonin reuptake inhibitors). While it is true that SSRIs such as fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram made a great contribution to the treatment of depressive symptoms, there are still so many points for improvement ; unsatisfied onset latency, side effect profiles and the treatment of non-responders.

Various approaches to overcome the limitation of SSRIs have introduced so far. Venlafaxine, duloxetine and milancipran were developed as dual uptake inhibitors at norepinephrine / serotonin transporter and bupropion at norepinephrine / dopamine transporter. Recently triple reuptake inhibitors (SNDRIs) are being developed in DOV pharmaceuticals, Sepracor and AMRI etc. Beside, some drugs such as mirtazapine and trazodone were developed by targeting receptors and/or monoamine transporters.

Preclinical animal studies can provide crucial information for drug discovery. So far a lot of tests to screen antidepressant-like activity of drug candidates have been developed. Some are often mechanism-based tests such as reserpine-induced ptosis and 5-HTP-induced head twitches. Others mimic depressive condition like behavioral despair tests and chronic mild stress. It is obvious that different screening flows should be applied to screen compounds with different types of targets. For examples, SSRIs such as fluoxetine showed strong dose dependency in 5-HTP-induced head twitches test and reserpine-induced ptosis test, but just weak significant effect in forced swimming test (FST). Even though moclobemide, a monoamine oxidase inhibitor, induced strong potentiation of 5-HTP-induced head twitches, it did not exhibit any efficacy in FST. In contrast, bupropion-like compounds had potent FST activity and no efficacy in 5-HTP-induced symptoms. To rule out the compounds with expected side profiles, it can be checked if the compounds induce the anti-cholinergic side effect (TCA-related side profile) in oxotremorine-induced tremor/salivation test or behavioral sensitization (psychostimulant-related side profile) in locomotor test.

SK-BioPharmaceuticals licensed out YKP10A, a novel antidepressant, to Janssen in 2000 (currently in phase II).