Pharmacology of Flibanserin

Franco Borsini1, Kennett Evans2, Kathryn Jason3, Frank Rohde1,
Barbara Alexander1, and Stephan Pollentier1

1 Boehringer Ingelheim Pharma KG, Biberach an der Riss, Germany;
2 Boehringer Ingelheim Pharmaceuticals, Burlington, Ontario, Canada;
3 Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA

Key Words: Flibanserin—Serotonin—Dopamine—Receptors—Firing rate—Adenylyl cyclase—Animal models—Antidepressants.

ABSTRACT

Flibanserin has preferential affinity for serotonin 5-HT1A, dopamine D4, and serotonin 5-HT2A receptors. In vitro and in microiontophoresis, flibanserin behaves as a 5-HT1A agonist, a very weak partial agonist on dopamine D4 receptors, and a 5-HT2A antagonist. In vivo flibanserin binds equally to 5-HT1A and 5-HT2A receptors. However, under higher levels of brain 5-HT (i.e., under stress), flibanserin may occupy 5-HT2A receptors in higher proportion than 5-HT1A receptors. The effects of flibanserin on adenylyl cyclase are different from those of buspirone and 8-OH-DPAT, two other purported 5-HT1A receptor agonists. Flibanserin reduces neuronal firing rate in cells of the dorsal raphe, hippocampus, and cortex with the CA1 region being the most sensitive in the brain. Flibanserin-induced reduction in firing rate in the cortex seems to be mediated through stimulation of postsynaptic 5-HT1A receptors, whereas the reduction of the number of active cells seems to be mediated through dopamine D4 receptor stimulation. Flibanserin quickly desensitizes somatic 5-HT autoreceptors in the dorsal raphe and enhances tonic activation of postsynaptic 5-HT1A receptors in the CA3 region. Flibanserin preferentially reduces synthesis and extracellular levels of 5-HT in the cortex, where it enhances extracellular levels of NE and DA. Flibanserin displays antidepressant-like activity in most animal models sensitive to antidepressants. Such activity, however, seems qualitatively different from that exerted by other antidepressants. Flibanserin seems to act via direct or indirect stimulation of 5-HT1A, DA, and opioid receptors in those animal models. Flibanserin does not display consistent effects in animal models of anxiety and seems to exert potential antipsychotic effects. Flibanserin may induce some sedation but does not induce observable toxic effects at pharmacologically relevant doses.