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Pharmacology of Flibanserin

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ABSTRACT

Flibanserin has preferential affinity for serotonin 5-HT_{1A}, dopamine D_4, and serotonin 5-HT_{2A} receptors. *In vitro* and in microiontophoresis, flibanserin behaves as a 5-HT_{1A} agonist, a very weak partial agonist on dopamine D_4 receptors, and a 5-HT_{2A} antagonist. *In vivo* flibanserin binds equally to 5-HT_{1A} and 5-HT_{2A} receptors. However, under higher levels of brain 5-HT (i.e., under stress), flibanserin may occupy 5-HT_{2A} receptors in higher proportion than 5-HT_{1A} receptors. The effects of flibanserin on adenylyl cyclase are different from those of buspirone and 8-OH-DPAT, two other purported 5-HT_{1A} 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-HT_{1A} receptors, whereas the reduction of the number of active cells seems to be mediated through dopamine D_4 receptor stimulation. Flibanserin quickly desensitizes somatic 5-HT autoreceptors in the dorsal raphe and enhances tonic activation of postsynaptic 5-HT_{1A} 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-HT_{1A}, 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.