

5-HT_{1A} Receptor Polymorphisms and Mental Illness

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Strong evidence supports an important role of the serotonin system in the etiology and treatment of mental illness. Genetic polymorphisms that affect the expression or function of key components of neurotransmitter systems or signaling cascades are believed to affect an individual's predisposition to psychiatric disorders. In addition to the SERT, 5-HT_{1A} receptors located on serotonergic cell bodies and dendrites play a critical role in the regulation of serotonergic neurotransmission. These 5-HT_{1A} receptors function as somatodendritic autoreceptors and when activated by 5-HT released from axon collaterals serve to inhibit serotonergic neuronal firing. Decreased serotonergic neurotransmission is associated with a number of mood disorders, e.g., bipolar illness, panic disorder, major depression and suicide. In response to antidepressant treatments, or long-term administration of novel anxiolytics such as Buspar® (Figure 15-8), 5-HT_{1A} somatodendritic autoreceptors become desensitized. Attenuation of 5-HT_{1A} somatodendritic autoreceptor sensitivity and function results in an increase in serotonergic neuronal firing rate and 5-HT neurotransmission, and is believed to contribute to the therapeutic effect of antidepressant drugs (Artigas et al., 2001; Blier et al., 2003). Post-synaptic 5-HT_{1A} receptors are also important components of antidepressant drug action, mediating behavioral and neurochemical responses to antidepressant treatments (De Vry, 1995; Mayorga et al., 2001; Santarelli et al., 2003).

A common C(1019)G polymorphism has been identified in the promotor region of the human 5-HT_{1A} receptor gene. This polymorphism is located in a sequence that is recognized by two transcription factors, Deaf-1 and Hes5, in an allele-dependent manner with the C-allele binding to these proteins but not the G-allele. Deaf-1 is co-localized with pre-and postsynaptic 5-

HT_{1A} receptors in brain, consistent with a role in the regulation of both pre- and postsynaptic 5-HT_{1A} receptors, but displays differential activity. In serotonergic cells, Deaf-1 suppresses 5-HT_{1A} receptor expression. In non-serotonergic cells, Deaf-1 exhibits enhancer activity. Both enhancer and repressor activities of Deaf-1 are abolished in the G-allele. The G-allele therefore is expected to result in decreased expression of postsynaptic 5-HT_{1A} receptors in forebrain areas and over-expression of 5-HT_{1A} autoreceptors on serotonergic neurons, which would translate to reduced serotonergic neuronal firing. The G-allele is associated with major depression, anxiety and panic disorder, and increased raphe 5-HT_{1A} binding potential in depressed patients. Increasing evidence supports a functional role for the C(-1019)G site in the dysregulation of 5-HT_{1A} receptor expression and predisposition to mental illness (Le François et al., 2008).

References

- Artigas, F., Celada, P., Laruelle, M., & Adell, A. (2001). How does pindolol improve antidepressant action? *Trends in Pharmacological Sciences*, *22*, 224–228.
- Blier, P., & Ward, N. M. (2003). Is there a role for 5-HT_{1A} agonists in the treatment of depression? *Biological Psychiatry*, *53*, 193–203.
- De Vry, J. (1995). 5-HT_{1A} agonists: recent developments and controversial issues. *Psychopharmacology*, *121*, 1–32.
- Le François, B., Czesak, M., Steubl, D., & Albert, P. R. (2008). Transcriptional regulation at a HTR1A polymorphism associated with mental illness. *Neuropharmacology*, *55*, 977–985.
- Mayorga, A. J., Dalvi, A., Page, M. E., Zimov-Levinson, S., Hen, R., & Lucki, I. (2001). Antidepressant-like behavioral effects in 5-hydroxytryptamine(1A) and 5-hydroxytryptamine(1B) receptor mutant mice. *J Pharmacol Exp Ther*, *298*, 1101–1107.
- Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., & Dulawa, S., et al. (2003).

Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*, 301, 805–809.