The P2X7 receptor and its genetic variants; relation to mood disorders

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The P2X7 receptor is a ligand-gated cation channel which is activated by extracellular ATP and which is highly expressed in monocyte-macrophages as well as microglia of the central nervous system. P2X7 is a two-transmembrane receptor with intracellular amino and carboxyl termini and is present as a trimer in cell membranes. Prolonged exposure to ATP induces a larger permeability state (dilated channel or pore) which allows influx of the large fluorescent cation, ethidium (314 Da) and which is used to measure receptor function. The P2X7 receptor is regarded as a pro-inflammatory receptor since its activation initiates a cascade of downstream signalling events including processing and secretion of interleukin-1β and interleukin-18 from macrophages and microglia. The P2RX7 gene resides on human chromosome 12q24.31, a region which has been associated with bipolar and depressive disorders in genetic linkage studies. The gene is highly polymorphic with at least 12 non-synonymous single nucleotide polymorphisms (SNPs) which change the function of the receptor. Recently three independent case-control studies from Canada, Germany and the UK have identified a SNP at nucleotide 1405 A>G in the gene which is strongly associated with both bipolar and major depressive disorders. This SNP is present in about 15% of the Caucasian population and changes Glutamine-460 to Arginine in the long carboxyl tail of the receptor but the function of this polymorphic variant is not known. We have genotyped over 3000 subjects to examine the linkage disequilibrium of the 1405 SNP with other functional polymorphisms in the gene. Site directed mutagenesis was used to introduce mutations into a human P2X7 plasmid both in isolation and in combination to recreate the 1405 G haplotypes found in the population. In isolation the Gln-460 to Arg mutation reduces P2X7 function but in combination with certain other mutations a dramatic increase in ATP-induced ethidium uptake is seen, suggesting that the 1405 variant may confer gain-of-function on the P2X7 receptor and this predisposes to bipolar disorders.