

RGS proteins: impact on the treatment of depression and anxiety

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Regulators of G protein signalling (RGS) proteins were first found to limit heterotrimer G protein signalling by accelerating the hydrolysis of GTP-bound to $G\alpha$ subunits, thereby terminating receptor pathway signalling. Subsequently, RGS proteins have been found to act as scaffolding proteins, to interact directly and selectively to G protein-coupled receptors (GPCRs) and to act as effector modulators (Ghavami *et al.* 2004; McCoy & Hepler, 2009). Through all of these interactions, RGS proteins act to negatively regulate signalling pathways. The selective interactions that occur among GPCRs, G proteins and RGS proteins provide an opportunity for more selective drug targeting to a specific complex of these proteins, (McCoy & Hepler, 2009; Shankaranarayanan *et al.* 2008) rather than the traditional approach of targeting GPCRs or more recent proposals for targeting RGS proteins. Targeting select GPCR/G protein/RGS complexes may prove useful for improving the treatment of depression.

Although major depression is a common disorder, treatment approaches for depression are woefully inadequate (Insel & Wang, 2009). Approximately one in six people in the USA suffer from major depressive disorder and individuals have a 16.2% lifetime prevalence for depression (Kessler *et al.* 2003). There are several classes of medications which are useful in the treatment of depression including selective serotonin reuptake inhibitors (SSRIs) and mixed norepinephrine/serotonin reuptake inhibitors. In fact, from recently published data on the top prescription drugs of 2010, two of these reuptake inhibitor anti-

depressants, escitalopram and duloxetine (Lindsley, 2011) are in the top 20 in sales in the USA. Despite the widespread use of antidepressant medications and especially reuptake inhibitors, there is a pressing need for better treatments for depression (Insel & Wang, 2009). The results from a major, large-scale clinical study, the Sequenced Treatment Alternatives to Relieve Depression trial emphasize three major problems with current antidepressant therapy. First, the current medications do not alleviate depression for a large percentage of patients. Second, when patients do respond to the medications, it takes weeks of therapy not hours or days as with most medications. Third, patients may respond to one antidepressant medication or combination of medications but not others and currently there are not methods to predict which medication or combination of medications will be effective for any individual (Insel & Wang, 2009; Kessler *et al.* 2003). It is therefore essential to identify new targets and new therapeutic approaches for the treatment of depression.

The paper 'Relationship between *Rgs2* gene expression levels and anxiety and depression-like behaviour in a mutant mouse model: serotonergic involvement' by Lifschytz *et al.* (2011) brings to our attention the importance of RGS protein modulation of receptor signalling in anxiety and depression. In their study, mice carrying a mutation in the RGS2 gene causing reduced expression levels were examined in several tests for anxiety and depressive-like behaviours. Mice homozygous for the RGS2 mutation demonstrated increased depressive-like behaviour while both heterozygotes and homozygotes displayed increased anxiety-like behaviours and reduced sociability. Linking their results to serotonin (5-HT)_{1A} receptor signalling was accomplished by demonstrating that the RGS2 mutant mice have reduced hypothermic responses to the 5-HT_{1A/7} receptor agonist, 8-hydroxy-2-dipropylaminotetralin (DPAT). The reduced hypothermic responses suggest that RGS2 is an important modulator of 5-HT_{1A} autoreceptor function in the raphe nucleus (Richardson-Jones *et al.*

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See Lifschytz *et al.* (2011). Relationship between *Rgs2* gene expression level and anxiety and depression-like behaviour in a mutant mouse model: serotonergic involvement (doi:10.1017/S1461145711001453).

2010). Furthermore, 5-HT_{1A} and 5-HT_{1B} mRNA expression levels were reduced in the raphe nucleus of the RGS2 mutant mice. 5-HT_{1B} and especially 5-HT_{1A} receptor signalling have a strong association with depression and anxiety and their treatments. It is important to note that RGS2 also modulates G_{q/11} coupled receptor signalling such as 5-HT_{2A/2C}, signalling pathways (McCoy & Hepler, 2009) which play a major role in depression and anxiety-like behaviours. Furthermore, previous studies have demonstrated that depression and anxiety-related neuropsychiatric disorders are linked to several single nucleotide polymorphisms (SNPs) in the RGS2 gene, one of which resulted in lower expression of RGS2 protein (Semplicini *et al.* 2006).

Recent reports suggest that 5-HT_{1A} receptors couple to different G α protein subunits and RGS proteins in other brain regions such as to G α _z/RGSZ1 in the hypothalamus to regulate neuroendocrine responses to DPAT (Serres *et al.* 2000) and to G α _{i2} in the hippocampus and cortex (Talbot *et al.* 2010). 5-HT_{1A} receptor signalling in each of these brain regions and signalling pathway complexes impacts on depression. Altered RGSZ1 expression in the hypothalamus may accelerate adaptive responses to treatment with SSRIs and thereby hasten the onset of antidepressant responses (Carrasco *et al.* 2004; Estrada-Camarena *et al.* 2006a,b). Drug development to selectively target particular 5-HT_{1A} receptor/G α /RGS protein complexes may provide an opportunity to selectively impact on a particular 5-HT_{1A} receptor pathway. Studies such as the one by Lifschytz *et al.* (2011) provide important underpinnings for the development of this type of selective targeting for the treatment for depression to provide relief for the large number of patients refractory to current therapeutic approaches and to hasten the onset of therapeutic effects.

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Statement of Interest

None.

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