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Invited review

Prevalence and influence of cys407* *Grm2* mutation in Hannover-derived Wistar rats: mGlu2 receptor loss links to alcohol intake, risk taking and emotional behaviour

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ABSTRACT

Modulation of metabotropic glutamate 2 (mGlu2) receptor function has huge potential for treating psychiatric and neurological diseases. Development of drugs acting on mGlu2 receptors depends on the development and use of translatable animal models of disease. We report here a stop codon mutation at cysteine 407 in *Grm2* (cys407*) that is common in some Wistar rats. Therefore, researchers in this field need to be aware of strains with this mutation. Our genotypic survey found widespread prevalence of the mutation in commercial Wistar strains, particularly those known as Han Wistar. Such Han Wistar rats are ideal for research into the separate roles of mGlu2 and mGlu3 receptors in CNS function. Previous investigations, unknowingly using such mGlu2 receptor-lacking rats, provide insights into the role of mGlu2 receptors in behaviour. The *Grm2* mutant rats, which dominate some selectively bred lines, display characteristics of altered emotionality, impulsivity and risk-related behaviours and increased voluntary alcohol intake compared with their mGlu2 receptor-competent counterparts. In addition, the data further emphasize the potential therapeutic role of mGlu2 receptors in psychiatric and neurological disease, and indicate novel methods of studying the role of mGlu2 and mGlu3 receptors.

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Abbreviations: mGlu2 receptor, metabotropic glutamate receptor 2; RGD, Rat Genomic Database.

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Contents

1. Introduction

The metabotropic glutamate 2 (mGlu2) receptor belongs to the family of G-protein coupled glutamate receptors that modulate transmission at synapses throughout the mammalian central nervous system, and that have been proposed as major targets for the development of drugs for human psychiatric and neurological diseases (Niswender and Conn, 2010; Nicoletti et al., 2011; Chaki et al., 2013; Li et al., 2015). The mGlu2 receptors signal through $G\alpha_{i/o}$ proteins inhibiting adenyl cyclase and reducing cAMP (Tanabe et al., 1992), cascading into effects on multiple systems including PKA/MAPK, GSK-3β, Src kinase, AMPA and NMDA receptors etc (Pin and Duvoisin, 1995; Harris et al., 2004; Trepanier et al., 2013; Wang et al., 2013). They also signal through Gβ/γ inhibiting calcium channels (Chavis et al., 1994; Scanziani et al., 1995) and activating potassium channels (Knoflach and Kemp, 1998; Chavez-Noriega et al., 2002). The major established physiological function of mGlu2 receptors is to modulate synaptic transmission as presynaptic auto- and hetero-receptors at glutamatergic and GABA-ergic terminals (Battaglia et al., 1997; Cartmell and Schoepp, 2000; Smolders et al., 2004). The perisynaptic location of mGlu2 receptors ideally positions them for sensing glutamate overflow (Petralia et al., 1996; Shigemoto et al., 1997) and release from astrocytes (Moran et al., 2005; Kalivas, 2009).

Such complexity of the actions of a single receptor subtype confounds attempts at predicting effects of exogenous agonists or antagonists of mGlu2 receptor on whole animal behaviours and hence their therapeutic potential. Nevertheless the predicted potential for mGlu2/3 receptor agonists based on limiting glutamate release has been borne out in animal models of schizophrenia (Schoepp and Marek, 2002), anxiety (Helton et al., 1998; Swanson et al., 2005), cerebral ischaemia (Bruno et al., 2001), epilepsy (Smolders et al., 2004), drug addiction (Kalivas, 2009) and chronic pain (Chiechio et al., 2010). There has also been some limited success with clinical studies (Grillon et al., 2003; Patil et al., 2007; Dunayevich et al., 2008) but this has not yet led to an approved drug. Clearly, the importance of understanding the role of mGlu2 receptors in physiology and pathology cannot be overstated.

One of the issues has been that orthosteric agonists and antagonists do not separate between mGlu2 and mGlu3 receptors (Nicoletti et al., 2011), which have different, and possibly opposing effects (Corti et al., 2007). To overcome this problem we recently used a new selective mGlu2 receptor agonist, LY395756, and its active enantiomer, LY541850 (Dominguez et al., 2005), to separate between the roles of mGlu2 and mGlu3 receptors in synaptic events (Ceolin et al., 2011; Hanna et al., 2013). However we found that many of the outbred Wistar rats studied were unresponsive to the selective mGlu2 agonist; this apparent anomaly was traced using Western blotting to the lack of mGlu2 receptor expression in some Wistar rats (Ceolin et al., 2011). Such animals being used for animal modeling of human diseases clearly produce misleading results when studying the roles of mGlu2 receptors. For example, mGlu2/3 agonists, known to reduce the phencyclidine-induced hyperlocomotion in other rat strains (Moghaddam and Adams, 1998; Cartmell et al., 2000; Monn et al., 2007), do not show this effect in Wistar rats lacking mGlu2 receptors (Wood et al., 2014).

Because of the demonstrated potential of the mGlu2 receptor as a therapeutic target, this finding is of critical importance to the research community. Immediately questions arise as to i) why is the mGlu2 receptor missing from some rats and ii) how frequently does this occur in populations of rats used in laboratory studies. We report here the occurrence of a single point mutation in exon 3 of the *Grm2* gene, which results in a premature stop codon at cysteine 407 of the mGlu2 receptor, and resultant loss of functional protein expression. We also report the high frequency of this mutant genotype in certain outbred and inbred rat lines that are commercially available or selectively bred, and we discuss its influence on behavioural characteristics.

2. Methods

2.1. Animals

For the initial studies, Wistar rats from Banting & Kingman Ltd.