Monash University researchers have identified GAD65 as a new anxiolytic drug target. The team has identified the structural mechanism that converts GAD65 from an inactive to active state. This knowledge could form the basis of a development program for creating novel, targeted therapies for anxiety and stress-related disorders.

**Benefits over existing therapies:**
- Potential to develop ‘First in Class’ anxiolytics that target GAD65
- Differentiated mechanism of action that is upstream of incumbent targets with potential for high efficacy and less side effects
- MOA where activity/inactivity of the target naturally restored

**Background**
Gamma-aminobutyric acid (GABA) is a key inhibitory neurotransmitter that modulates neuronal excitability in relation to stimulation and stress. Anxiety-related disorders such as panic disorder and post traumatic stress disorder are commonly associated with low levels of GABA. In humans, two isoforms of the pyridoxal phosphate (PLP; Vitamin B6) dependent decarboxylase Glutamic Acid Decarboxylase (GAD65 and GAD67) are responsible for total GABA synthesis from the excitatory neurotransmitter Glutamic Acid (1).

GAD65 – A New Target for Anxiolytics

The two isoforms of GAD have distinct and different physiological roles. Studies indicate that GAD67 predominantly exists in an active (holo) state and appears to be responsible for basal production of GABA. GAD65 exists predominantly in an inactive (apo) state, and is able to produce GABA activated by cofactor binding and activation. Therefore, GAD65 appears to be able to produce GABA in response to stress.

Consistent with this, GAD65 knockout mice exhibit a general anxiety disorder phenotype and exhibit increased fear behaviour (2,3). Furthermore, GAD65 knockout mice are insensitive to drugs such as diazepam that facilitate the actions of released GABA. This suggests that GAD65-generated GABA is crucial in modulating anxiety-related responses to anxiogenic stimuli (4).

Current pharmacological treatments for anxiety-related disorders are in the GABA receptor or SSRI modulator class and are suboptimal because they result in side effects such as sedation, and require prolonged use, which could result in patients developing tolerance or resistance to the treatment and/or dependence and abuse. Identifying a therapeutic molecule that can modulate the activity of GAD65 offers the benefits of specific action at the site of GABA production, and a defined period of treatment with a potential to restore that natural balance of GAD65 in the patient.

**The Opportunity**
Monash Researchers have identified the structural basis for auto-regulation of GAD function (5,6). Critically, they have shown that GAD65 contains a flexible catalytic loop region, which results in rapid auto-inactivation of the enzyme. In contrast, GAD67 was shown to have a stabilized catalytic loop region, which enables it to remain active. Therefore, stabilising the catalytic loop region, preferably transiently, will allow dramatic increase in GABA production levels.

The team has gained valuable structure/activity know-how of the target and mechanism of function. This knowledge could form the basis of a development program for creating novel, safe and effective anxiolytic drugs that modulate GAD65 activity by stabilising the catalytic loop region of the enzyme.

Monash University is seeking a partner to create and test compositions that could stabilise the catalytic loop region of GAD65. The Monash research team has extensive experience in all aspects of preclinical development from peptide chemistry, structural biology and cellular biology with in vitro analysis and in vivo integrative function.


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