Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

Metabotropic glutamate receptors as drug targets for the treatment of absence epilepsy

Richard Teke Ngomba[1] and Gilles van Luijtelaar[2]

Metabotropic glutamate (mGlu) receptors are expressed in key regions of the cortex and the thalamus and are known to regulate spike and wave discharges (SWDs), the electroclinical hallmarks of absence seizures. Recent preclinical studies have highlighted the therapeutic potential of selective group I and III mGlu receptor subtype allosteric modulators, which can suppress pathological SWDs. Of particular interest are positive allosteric modulators (PAMs) for mGlu5 receptors, as they currently show the most promise as novel anti-absence epilepsy drugs. The rational design of novel selective positive and negative allosteric mGlu modulators, especially for the mGlu5 receptor, has been made possible following the recent crystallographic structure determination of group I mGlu receptors. Our current knowledge of the role of different mGlu receptor subtypes in absence epilepsy is outlined in this article.

Addresses
[1] School of Pharmacy in College of Science, University of Lincoln, Lincoln LN6 7TS, UK
[2] Donders Centre of Cognition, Radboud University, Nijmegen, The Netherlands

Corresponding author: Ngomba, Richard Teke (richardngomba@hotmail.com, rngomba@lincoln.ac.uk)

Current Opinion in Pharmacology 2018, **38**:43–50

This review comes from a themed issue on **Neurosciences**

Edited by **Ferdinando Nicoletti, Valeria Bruno** and **Giuseppe Battaglia**

https://doi.org/10.1016/j.coph.2018.01.012

Introduction

Absence epilepsy is non-convulsive and is characterized by a sudden decrease in responsiveness, accompanied by staring and the simultaneous appearance of highly stereotypical bilateral symmetrical network activity in the form of spike-and-wave discharges (SWDs) in the EEG. The main anatomical structure where these SWDs are generated is the extensive cortico–thalamo–cortical network which includes the reticular thalamic nucleus (nRT) [1•,2,3•,4]. The frontal cortex has been identified as the major initiation site for SWDs in some patients [5], although other cortical locations including the temporal, occipital and parietal lobe can also be initiation sites [6]. In a widely used and validated genetic absence animal model, the WAG/Rij strain of rat, the peri-oral region of the somatosensory cortex (S1po) has been identified as the SWD initiation site [5,7•]. These WAG/Rij rats are an inbred strain that shows an age-dependent increase in the probability of developing spontaneous SWDs. Following their development, SWDs increase in both frequency and mean duration. SWDs occur mainly during passive wakefulness, in an otherwise motionless animal, not during deep slow wave sleep. During SWDs, animals do not make overt behavioural responses to obtain food pellets, as they would do normally suggesting that responsiveness is reduced.

Many classical and newer antiepileptic drugs have been tested in this and in a similar absence model, the GAERS (Genetic absence epilepsy rats from Strasbourg). Based on the outcomes of such experiments, it has been concluded that these animal models provide a good prediction of the efficacy of drugs and the possible off-target effects that will be observed in humans with absence seizures [3•].

The glutamatergic and GABAergic systems are involved in controlling excitation and inhibition respectively, in the cortex and thalamus. Aside from the highly excitable site in the cortex that initiates SWDs in WAG/Rij rats and in GAERS, increased thalamic tonic GABAergic inhibition has also been demonstrated in some genetic absence epilepsy models [7•,8•]. The fact that metabotropic glutamate (mGlu) receptors are expressed in different regional circuit cell types within cortico-thalamo-cortical networks, and that they modulate synaptic transmission [9•,10,11] (see also Figure 1), suggest a potential role for mGlu receptors in regulating SWDs.

The mGlu receptors are classified into three main groups (I, II and III), and pre-clinical studies to date have shown that ligands for the different receptor subtypes in each group have anti-absence properties [12•,13–15,16•,17–19].

Furthermore, interest in identifying new mGlu receptor ligands with anti-absence properties has been encouraged by the discovery of distinct allosteric binding sites in the crystallographic structure of transmembrane domains in group I mGlu receptors (mGlu1 and mGlu5 receptors), permitting a rational design of specific compounds [20•,21•]. Here, we focus on the role of mGlu receptors

Figure 1

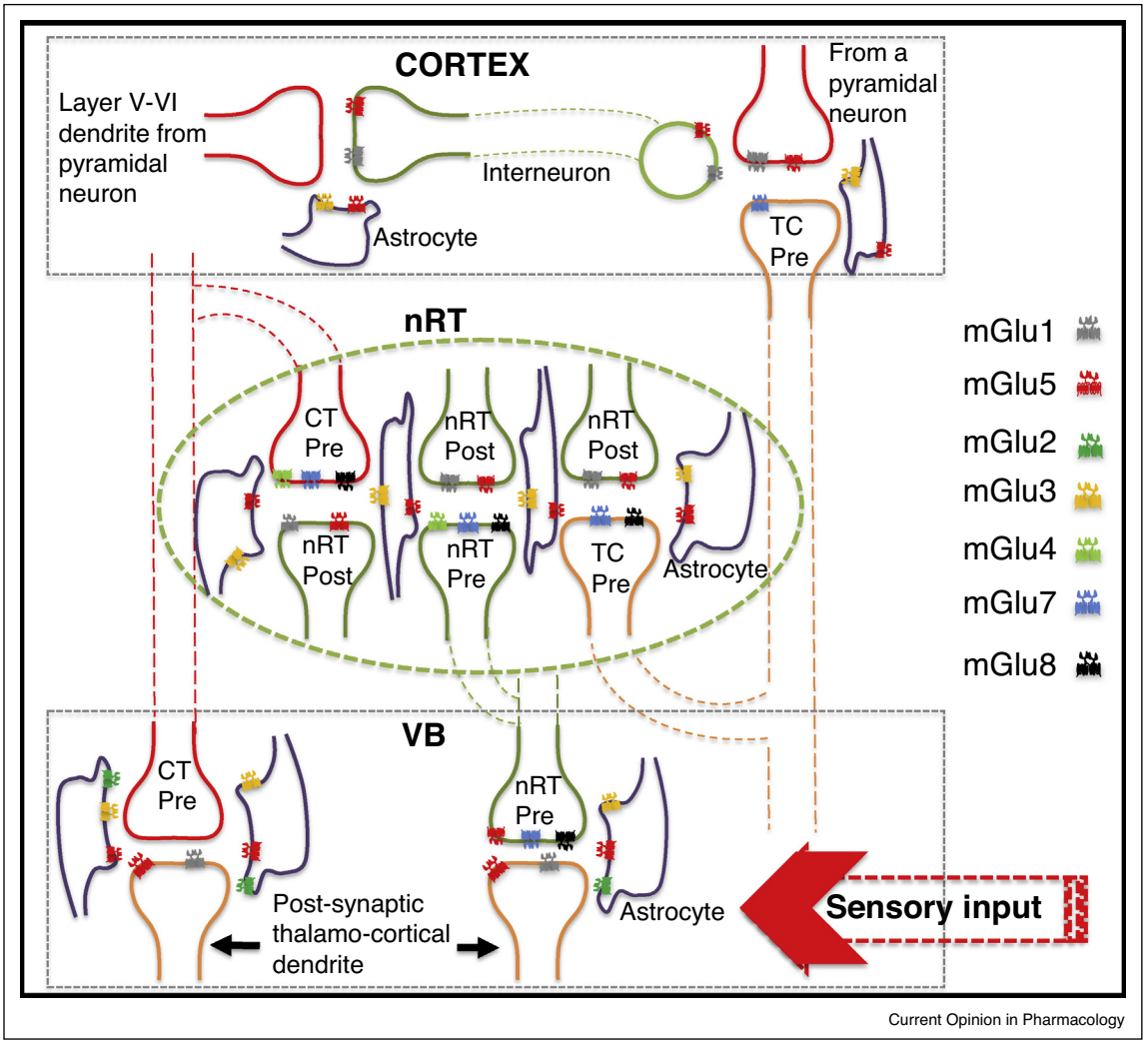

Diagram showing synaptic localization of mGlu receptor subtypes in the modulation of absence seizures. In red, dendritic spine from the pyramidal cell (e.g. layer IV), cortico-thalamic (CT) glutamatergic projection into the ventrobasal thalamus with collateral onto the reticular thalamic nucleus (nRT). Glutamatergic thalamic relay neuron (TC) sends projection (in orange) to the deep layers of the cortex (e.g. layer VI) and collateral onto the nRT. GABAergic nRT neuron in green, sending projection to the VB and collateral back onto the nRT. The synapses are mostly surrounded by astrocytic processes (in purple) expressing distinct mGlu receptor subtypes (principally mGlu3 and mGlu5) as indicated by the different colours. The sensory afferents at the thalamus are depicted as a large red arrow. mGlu1 and mGlu5 receptors (also present on astrocytes) are located perisynaptically at excitatory synapses. Group II receptors (mGlu2 and 3) are present in both cortical and thalamic synaptic terminals. mGlu3 receptors are expressed in astrocytes, and the activity of mGlu2 has recently been identified on astrocytes by a combination of electrophysiological and pharmacological methods. Subtypes of mGlu4, 7 and 8 are usually localized presynaptically at active regions.

and their allosteric modulators as studied in the WAG/Rij rat model of absence epilepsy [3•].

Localization and modulation of mGlu receptors in the cortico–thalamo–cortical circuitry

The classification of mGlu receptors into groups is based on their pharmacological properties and amino acid sequence homology profile [12•,22,23]. These receptors are coupled to different G proteins and they modulate slow postsynaptic neuronal responses, either through the presynaptic or postsynaptic machinery or through modulating astrocytes function [9•,10,11,12•,24] (see also Figure 1).

Group I mGlu receptors

mGlu1 and mGlu5 receptor subtypes are members of group I and they are coupled to Gq/G_{11} proteins, which upon activation trigger polyphosphoinositide hydrolysis leading to the production of inositol-1,4,5-trisphosphate and diacylglycerol. These receptors are also able to regulate the activity of different types of Ca^{2+} and K^{+} channels