Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol8Issue1abst093P.pdf

$GABA_B$ receptor subtypes differentially modulate chemoconvulsant-induced seizure

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Epilepsy is a neurological disorder caused by imbalanced excitatory and inhibitory activities in the brain. $GABA_B$ receptors are the G-protein-coupled receptors for the inhibitory neurotransmitter GABA and its activation modulate both the excitatory and inhibitory synaptic transmission in the brain. $GABA_B$ receptors are strongly implicated in the genesis and spread of seizures[1], however, the precise roles of $GABA_B$ receptor subtypes that are located at different synaptic compartments[2] and neuronal networks are yet to be defined. In mice lacking either the $GABA_{B1a}$ or $GABA_{B1b}$ isoforms[2], we examined the roles of the $GABA_{B(1a,2)}$ and $GABA_{B(1b,2)}$ receptors in the development of seizure.

Epileptic behaviours in mice were triggered by an injection (subcutaneous route at 60 mg/kg) of a chemoconvulsant pentylenetetrazol (PTZ). Epileptic behaviours were monitored for 45 min and scored according to the modified severity scale (1, hypoactivity; 2, partial seizures; 3, generalised seizures; 4, tonic-clonic seizures; 5, mortality due to seizure). To examine the origin of the differences in epileptic behaviour, distributions of the $GABA_{B(1a,2)}$ and $GABA_{B(1b.2)}$ receptors in the brain were examined by immunolabelling of $GABA_{B1}$ and $GABA_{B2}$ proteins. In addition, the Schaffer collateral-CA1 field excitatory postsynaptic potentials (fEPSPs) and population spikes, were recorded using a multi-eletrode array system (MED64) in hippocampal slices and the modulation by $GABA_B$ receptor activation was examined [3].

Seizures behaviours developed immediately after the injection of PTZ and progressed with increasing severity according to the scale. The mean maximum seizure scores were found to be 3.2±0.2 for wild-type mice, 4.8±0.2 for $GABA_{B1a}^{-/-}$ and 3.3±0.3 for $GABA_{B1b}^{-/-}$ mice, showing significantly increased seizure severity in the $GABA_{B1a}^{-/-}$ mice ($p<0.01$, one-way ANOVA). The $GABA_{B(1a,2)}$ receptors may, therefore, be essential for the control of seizure activity. Functional heteromeric $GABA_B$ receptors labelled by the $GABA_{B2}$ antibody showed that the expression of $GABA_{B(1a,2)}$ receptors in the $GABA_{B1b}^{-/-}$ mice was uniform across the brain, but in the $GABA_{B1a}^{-/-}$ mice, the $GABA_{B(1b,2)}$ receptors were absent in the caudate putamen, globus pallidus, amygdala and CA3 stratum lucidum, which are brain areas potentially involved in the genesis and spread of seizure activities. $GABA_{B(1a,2)}$ receptors in these brain regions may, therefore, be essential for the control of seizure. In addition, in $GABA_{B1a}^{-/-}$ mice, neither the fEPSPs or the population spike were significantly inhibited by the $GABA_B$ receptor agonist, baclofen (50 μM, 95.0 ± 11.7 % of control); whereas baclofen significantly inhibited these activities in the wildtype (16.3 ± 3.2 % of control) and $GABA_{B1b}^{-/-}$ mice (34.6 ± 4.3 % of control), confirming an essential role for the $GABA_{B(1a,2)}$ receptors in heterosynaptic inhibition.

In conclusion, the $GABA_{B(1a,2)}$ receptor subtype is shown to play an essential role in the control of chemoconvulsant-induced seizure. The anatomical and synaptic localisation of the subtype may be responsible for the action. It is possible that deficits in the transcriptional and posttranslational mechanisms for $GABA_{B1a}$ isoforms could lead to increased seizure susceptibility.

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