**Monitor Editor:** Matthew Thorne
m.thorne@elsevier.com

# monitor


## MOLECULES

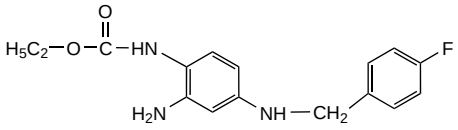
### Retigabine: a novel anticonvulsant drug in development

Retigabine, *N*-[2-amino-4-(4-fluorobenzylamino) phenyl] carbamic acid ethyl ester **(i)**, a clinical drug candidate [1] in development for the treatment of epilepsy, successfully completed a Phase II clinical trial with the FDA. Epilepsy is a neurological disorder characterized by excessive electrical discharge in brain, which causes seizures. The therapeutic strategy in countering epilepsy involves reducing neuronal excitability through different mechanistic pathways. The majority of the therapeutics currently used in the treatment of epilepsy is either directed towards blocking voltage-gated sodium and calcium ion channels or potentiating γ-amino butyric acid (GABA)-mediated neurotransmission, with little focus on voltage-gated potassium ion channels, despite these channels having a major role in the control of all aspects of neuronal excitability (functional impairment of potassium ion channels, either by mutation or inhibition, results in epilepsy [2]).

Retigabine is a novel broad spectrum anticonvulsant [3] that activates voltage-gated potassium ion channels (subfamily Q: genes *KCNQ1–KCNQ5*; and proteins $K_v7.1$–$K_v7.5$). To date, five members of subfamily Q have been cloned, four of which are involved in hereditary diseases (*KCNQ1–KCNQ4*). A recent study showed that retigabine facilitates the voltage-dependent opening of KCNQ2 by binding to its activation gate [4]. Activation of potassium ion channels represents a new means of reducing excessive neuronal activity. Mutational studies of KCNQ2 indicate that retigabine binds to the hydrophobic pocket between cytoplasmic transmembrane segments S5 and S6 [4]. The molecular mechanism underlying the activity of retigabine is not yet fully understood. Identification of the molecular targets of retigabine will facilitate the efficient exploitation of retigabine as a 'lead compound'.

In addition to acting on potassium ion channels, retigabine also affects GABA neurotransmission in the $GABA_A$ receptor [5], which is a key inhibitory receptor in the central nervous system and is implicated in epilepsy. Malfunction of the $GABA_A$ receptor leads to hyperexcitability in the brain, which causes seizures, making this receptor an important target for antiepileptic therapeutics. Apart from increasing the concentration of GABA in the brain (by either enhancing GABA synthesis or blocking GABA metabolism), retigabine allosterically potentiates GABA-induced current in rat cortical neurons in a concentration-dependent manner [5]. Furthermore, compared with other antiepileptic therapeutics, retigabine is unique in that it selectively activates potassium ion channels $K_v7.2$–$K_v7.5$ and not cardiac $K_v7.1$, thereby avoiding cardiac side effects [4].

Recent advances in molecular genetics identified many epilepsy-causing mutations in ion-channel membrane-bound proteins (ligand-gated and voltage-gated [6]). Epilepsy gene hunting is expected to lead to a rational therapy based on a better understanding of human epileptogenesis at a molecular level. Screening for novel antiepileptic drugs using these epilepsy-linked mutated ion channels is expected to result in syndrome-specific treatment with minimal side effects. Moreover, testing anticonvulsants, such as retigabine, on these epileptic receptors will help in understanding the activity of the drug in countering different types of epilepsy.




**(i)**

1 Ferron, G.M. *et al.* (2002) Multiple-dose, linear, dose-proportional pharmacokinetics of retigabine in healthy volunteers. *J. Clin. Pharmacol.* 42, 175–182
2 Rundfeldt, C. (1997) The new anticonvulsant retigabine (D-23129) acts as an opener of K+ channels in neuronal cells. *Eur. J. Pharmacol.* 336, 243–249
3 Rostock, A. *et al.* (1996) D-23129: a new anticonvulsant with a broad spectrum activity in animal models of epileptic seizures. *Epilepsy Res.* 23, 211–223
4 Wuttke, T.V. *et al.* (2005) The new anticonvulsant retigabine favors voltage-dependent opening of the Kv7.2 (KCNQ2) channel by binding to its activation gate. *Mol. Pharmacol.* 67, 1009–1017
5 Rundfeldt, C. and Netzer, R. (2000) Investigations into the mechanism of action of the new anticonvulsant retigabine. Interaction with GABAergic and glutamatergic neurotransmission and with voltage-gated ion channels. *Arzneimittelforschung* 50, 1063–1070
6 Noebels, J.L. (2003) The biology of epilepsy genes. *Annu. Rev. Neurosci.* 26, 599–625

***Kannan Sivaprakasam***
***Latha Ramakrishnan***
*ks248@cornell.edu*




1359-6446/05/$ – see front matter  PII: S1359-6446(05)03532-4