RETIGABINE: LESSER - KNOWN EFFECTS IN PRECLINICAL STUDIES

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ABSTRACT

Retigabine is a novel anticonvulsant with unique mechanism of action. It induces hyperpolarization of the neuronal membrane by activating a specific type of potassium channels (Kv7, KCNQ). Retigabine is approved by EMA as "adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy". The purpose of this review is to resume lesser – known effects of Retigabine, evaluated in preclinical studies. Data, based on preclinical tests revealed efficacy in different pain models. Other studies suggest neuroprotective effect. Retigabine showed also myorelaxant action and antimanic potential. It may have also antipsychotic properties. The results reveal new possibilities of application in different therapeutic fields.

Key words: *Retigabine, Kv7, Pain, Myorelaxation, Mania, Review*

Introduction.

Retigabine (Fig. 1.) is a novel antiepileptic drug approved by the European Medicines Agency under the trade name *Trobalt*® on March 28, 2011. Retigabine is approved by EMA as "adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy" [23]. It is a broad spectrum anticonvulsant with multiple mechanisms of action.

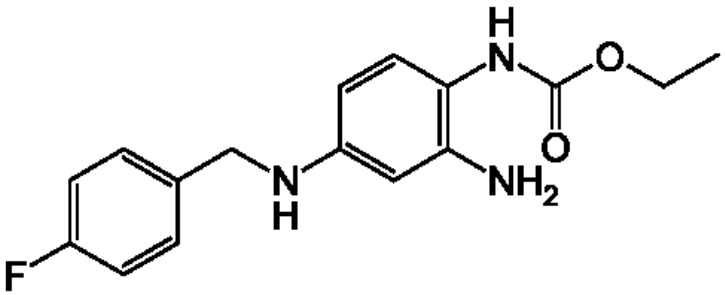

Figure1. Retigabine – chemical structure.

Mechanisms of action.

The main mechanism is related to the neuronal potassium channels. Retigabine acts as activator of low-threshold voltage gated K^+ channels (Kv). The Kv7 family of potassium channels includes 5 members – Kv7.1, Kv7.2, Kv7.3, Kv7.4 and Kv7.5. Kv7.1 is expressed in cardiomyocytes, and Kv7.2 – Kv7.5 - in neurons [20]. Voltage-gated K+ channels (M-channels) in most neurons are composed of Kv7.2 and Kv7.3 subunits. Their function is under the influence of muscarinic acetylcholine receptor. The binding of acetylcholine to its receptor leads to closing of the potassium channel and depolarization of the membrane. Retigabine acts as activator of K+ channels, consisting of Kv7.2 – Kv7.5 subunits, but does not influence Kv7.1 in the cardiac muscle, as reviewed by Splinter M., 2012 [20].

Kv7.4 subunits are expressed in nigrostriatal and mesolimbic pathways and according to Hansen H.H. et al. (2006) Retigabine reduces the synthesis of dopamine in striatal neurons [7].

Another mechanism involves GABA-induced currents. Retigabine acts on $GABA_A$ receptors and increase the postsynaptic Cl^- current [16]. It blocks GABA metabolism [18] and increases the synthesis of this inhibitory neuromediator [12]. The drug induces changes in the levels of excitatory amino-acids.

Treatment with Retigabine leads to significantly lower concentrations of glutamate and glutamine in mouse brain [18].

Pain models

Retigabine showed efficacy in two models of neuropathic pain – chronic constriction injury and spared nerve models in response to pin prick stimulation. In the formalin test, Retigabine (20 mg/kg, p.o.) was effective only in the second phase. Retigabine influenced cold sensitivity chronic constriction injury model [1].

Retigabine was effective at doses higher than 5 mg/kg p.o. in tail-flick test, performed on rats [6]. This result showed its activity in an acute pain model in rats. According to Blackburn-Munro and Jensen (2003) Retigabine had no effect in this test. This difference may be caused by the different methodology used in both cases [6].

The same autors showed that Retigabine can influence the hypersensitivity caused by ligation of the L5 spinal nerve – a model of neuropathy. The anti-hyperalgesic effect was significant after administration of 10 and 20 mg/kg Retigabine [6].

The results revealed that the drug may be effective in the treatment of acute and chronic pain.

Neuroprotective activity

According to Rekling JC (2003) Retigabine has no neuroprotective effect in rat hippocampal slice cultures exposed to oxygen/glucose deprivation up at concentration 300μM [17].

Boscia F et al. (2006) in contrast found the drug as effective neuroprotective agent, preventing the neuronal death in the dentate gyrus of hippocampus in vitro . The mechanism of this effect may be its antioxidant activity, but it has no relation to the potassium channels [2].

In vivo experiments showed that Retigabine prevents peripheral neuropathy caused by Cisplatin. The neuroprotective effect was evaluated when the drug was administrated intraperitoneally at a dose of 10 mg/kg 30 minutes before the administration of Cisplatin [15].

Myorelaxation

Kv7 channels are found in smooth muscle cells of different organs in rodents and humans. Retigabine is found to cause in vitro myometrial relaxation in mouse and human, while administration of Kv7 inhibitor leads to spontaneous myometrial contractions [14].

Joshi S. et al. (2009) investigated the influence of Retigabine in isolated pulmonary artery smooth muscle cells and in vivo on rats. These cells express Kv7.4 and a small amount of Kv7.1 and Kv7.5 potassium channels. The vasodilatator effect of Retigabine suggests that the drug may be effective in treatment of pulmonary hypertension [11].

Voltage-gated potassium channels were found in different cell types of the gastrointestinal tract. In the rat proximal stomach they appear to modulate the resting muscle tone. Treatment with Kv7 channel openers leads to relaxation of the gastric smooth muscle [10].

Kv7.1, Kv7.4 and Kv7.5 subunits were found in cells in blood vessels. Application of Retigabine leads to vasorelaxation of vessels, when contractions were induced by phenylephrine [22].

Increased micturition volume and voiding intervals were evaluated after intravenous, intracerebroventricular and intravesical administration of Retigabine and the drug may be useful in the treatment for detrusor overactivity in humans [21].

Smooth muscle cells in the airways in human and guinea pig express also Kv7 channels. It was found that histamine suppress Kv7 currents in airway myocytes and leads to bronchoconstriction. Kv7 channel openers may be effective as bronchodilators and may relieve airway hyperconstriction in asthma or other airway diseases [3].

Kv7.2, Kv7.3 and Kv7.4 channels were detected in human skeletal muscle cells. As an opener of Kv7.2-5 channels Retigabine induces myoprotection and reversal of mevastatin-induced myotoxicity [9].

Antimanic effect

Retigabine is effective in amphetamine and amphetamine+chlordiazepoxide hyperactivity model in mice. The antimanic activity is probably related to its influence on dopaminergic (DA) transmission

[7]. According to Dencker D (2010) the drug has normalizing effect on this transmission [4]. In the amphetamine+chlordizepoxide model Retigabine attenuates the hyperactivity at dose 1 mg/kg s.c. without to influence the motor activity [5].

The drug attenuates the increased locomotor activity induced by cocaine, phencyclidine and methylphenidate at doses higher than 1 mg/kg i.p. [8].

Moreover Retigabine inhibits glucose metabolic activity in CNS – effect observed in standard mood stabilizing agents. The data reveal the potential of Retigabine in treatment of bipolar disorder [13].

Retigabine as antipsychotic

Sotty F. et al. (2009) revealed the potential of Retigabine as a new antipsychotic. In vivo and in vitro studies showed that Retigabine inhibits the excessive DA neurotransmission. In contrast to the other antipsychotics the drug does not have influence on postsynaptic D2 neurons and may have better tolerability [19].

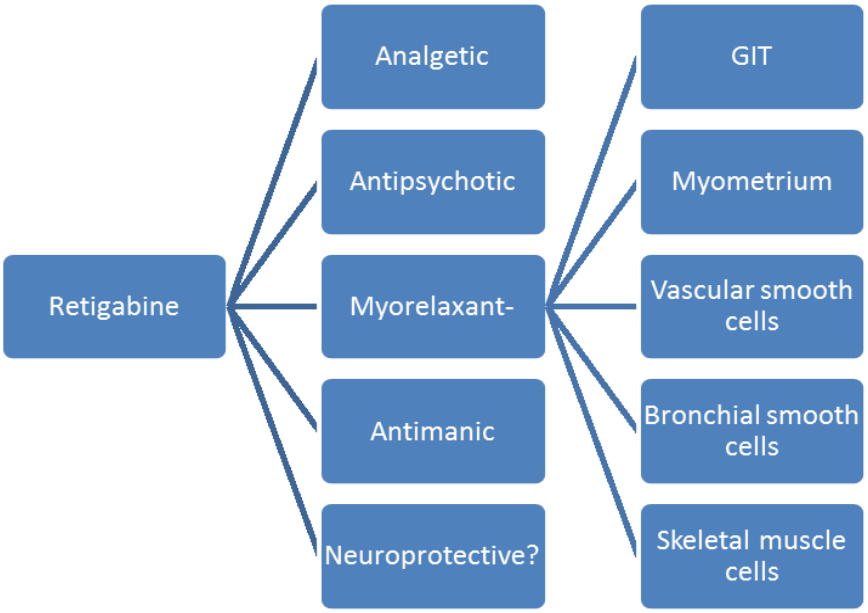

Figure 2. Lesser - known effects of Retigabine.

Conclusion.

Retigabine, a voltage-gated potassium channel opener, currently used as anticonvulsant may be useful in treatment in other deseases. Preclinical studies indicated efficacy in treatment of neuropathic and acute pain. The drug may be also neuroprotector. Application of Retigabine leads to myorelaxation of smooth muscle cells in different tissues. Other indications for clinical use may be bipolar disorder and psychosis (Fig. 2).

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