Nature Reviews Neurology | Published online 16 Dec 2015; doi:10.1038/nrneurol.2015.235

EPILEPSY

Early treatment could prevent genetic epilepsy in mice

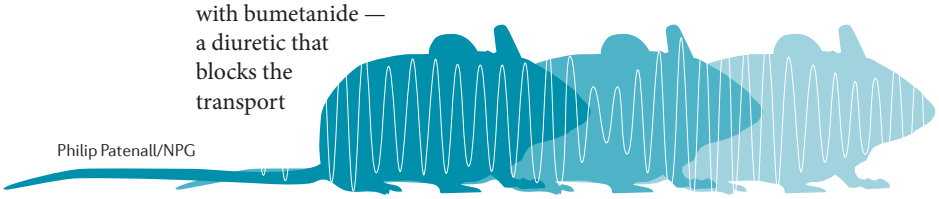
> treatment timing is critical for switching off epileptogenesis

Restoration of chloride homeostasis in young mice with K_V7 voltage-gated K^+ channel dysfunction prevents epileptogenesis, and normalizes circuit function and behaviour in adult mice, according to new research published in *Nature Medicine*. "Our work is the first to demonstrate that treatment during a specific window of vulnerability can prevent the manifestation of a genetic disease," says Dirk Isbrandt, who led the study.

In humans, mutations in K_V7 channels are associated with benign idiopathic epilepsy syndromes and severe neonatal epileptic encephalopathy. Isbrandt and colleagues used a mouse model with dysfunctional K_V7 channels to assess whether restoration of chloride homeostasis with bumetanide — a diuretic that blocks the transport of Na^+, K^+ and Cl^- ions — during early development could prevent development of epilepsy.

The researchers treated K_V7-deficient and control mice with bumetanide during the first two postnatal weeks. The treatment normalized neuronal network activity and prevented development of structural and behavioural pathology in K_V7-deficient mice. Bumetanide did not adversely affect control mice.

In a previous study, the researchers had discovered that restoration of K_V7 K^+ currents at a later developmental stage (10–12 weeks) does not prevent development of epilepsy. "Together, our data indicate that treatment timing is critical for switching off epileptogenesis," Isbrandt concludes.



Philip Patenall/NPG

The postnatal period during which the investigators treated the mice roughly corresponds to the third trimester of pregnancy in humans. "The treatment of human neonates at an equally early developmental would, thus, be feasible for preterm infants, who are at high risk of developing epilepsy," Isbrandt comments. The safety of bumetanide in preterm infants has not been established but, according to Isbrandt, potentially safer and more-effective alternatives are currently being developed.

In the meantime, the researchers plan to investigate whether similar windows of opportunity for treatment exist for other genetic epilepsies, such as the Na^+ channel mutations implicated in Dravet syndrome.

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ORIGINAL ARTICLE Marguet, S. L. *et. al.* Treatment during a vulnerable developmental period rescues a genetic epilepsy. *Nat. Med.* http://dx.doi.org/10.1038/nm.3987