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NEUROLOGICAL DISORDERS

MicroRNA gets motoring

MicroRNA-128 (miR-128) is widely and abundantly expressed in the postnatal developing brain, but its function is not well understood. A new study by Tan *et al.* reveals that miR-128 plays a crucial part in the regulation of the excitability of dopamine D1 receptor-expressing neurons (D1 neurons) in the striatum.

Two genes encode miR-128, *mir-128-1* and *mir-128-2*, but it is *mir-128-2* that accounts for most miR-128 expression in the brain. Juvenile mice in which *mir-128-2* is selectively silenced in forebrain neurons exhibit motor hyperactivity, seizures and death at 2–3 months of age. D1 neurons regulate motor behaviour in mice and humans, and when the authors generated mice lacking *mir-128-2* selectively in D1 neurons, they found a similar fatal epilepsy phenotype to that observed in mice lacking *mir-128-2* selectively in the forebrain. To identify the targets of *mir-128-2* that mediate this seizure activity, Tan *et al.* used a combination of translating ribosome affinity purification (TRAP) and bioinformatic network and pathway analyses. They found that *mir-128-2* regulates the expression of many ion channels and transporters, as well as other genes that contribute to neurotransmitter-driven neuronal excitability, motor activity and epilepsy in humans.

Among the targets of *mir-128-2* were several components of the extracellular signal-regulated kinase 2 (ERK2; also known as MAPK1) signalling network, which has an important role in neuronal excitability. The authors found that D1 neurons lacking *mir-128-2* showed increased ERK2 activation and increased dendritic excitability compared with controls. ERK2 overactivation is associated with increased motor activity and seizures in mice, suggesting that excessive activation of the ERK2 pathway might underlie the motor hyperactivity and fatal epilepsy that is observed in mice lacking *mir-128-2*.

Interestingly, increased ERK2 activation has also been detected in D1 neurons of mice with chemically induced Parkinson's-like disease. Hypersensitivity of D1 neurons to dopamine was found in both mice lacking *mir-128-2* in D1 neurons and mice with Parkinson's-like disease. Importantly, the authors found that increased miR-128 expression in adult mouse forebrain neurons protects against abnormal motor activities associated with chemically induced Parkinson's disease. These findings suggest a role for *mir-128-2* in motor disorders and epilepsy.

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ORIGINAL RESEARCH PAPER Tan, C. L. *et al.* MicroRNA-128 governs neuronal excitability and motor behavior in mice. *Science* **342**, 1254–1258 (2013)

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