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PARATHYROID FUNCTION

# KEY ROLE FOR DICER-DEPENDENT miRNAS

A new study shows that increased production of parathyroid hormone (PTH) by the parathyroid glands in response to hypocalcaemia and uraemia is dependent on endonuclease dicer and microRNA (miRNA) maturation. As secondary hyperparathyroidism—the excessive production of PTH in response to hypocalcaemia or uraemia—is a frequent complication of chronic kidney disease, the findings might lead to new strategies for the management of secondary hyperparathyroidism in patients with renal disease.

The researchers, led by Tally Naveh-Many, generated parathyroid-specific *Dicer1* knockout (*Dicer1*$^{PT-/-}$) mice and subjected them to acute hypocalcaemia (induced by intraperitoneal injection of ethylene glycol tetraacetic acid). Whereas serum levels of PTH increased fivefold in control mice, no increase was observed in *Dicer1*$^{PT-/-}$ mice, which demonstrates that Dicer1 and Dicer1-dependent miRNAs are essential for the increased PTH secretion induced by acute hypocalcaemia. *In vitro* culturing of parathyroid gland tissue in a low-calcium medium confirmed the *in vivo* findings: PTH secretion increased 20-fold in explant cultures from control mice, whereas the response was substantially diminished in those from *Dicer1*$^{PT-/-}$ mice.

Chronic hypocalcaemia (induced by feeding weanling mice a calcium-depleted diet for 3 weeks) also induced less PTH secretion in *Dicer1*$^{PT-/-}$ mice than in control mice. Under the same conditions, PTH secretion was also impaired in heterozygous *Dicer1*$^{PT+/-}$ mice compared with controls, indicating that *Dicer1* haploinsufficiency is enough to abrogate the response of the parathyroid glands to hypocalcaemia. Uraemia (induced by feeding mice an adenine high-phosphorus diet) also reduced the PTH response in *Dicer1*$^{PT-/-}$ mice compared with controls, which indicates that development of secondary hyperparathyroidism due to both uraemia and chronic hypocalcaemia is reliant on Dicer1-dependent miRNAs.

Going forward, the researchers plan to identify the specific miRNAs and their target mRNAs in the parathyroid gland that mediate the increased expression of PTH in secondary hyperparathyroidism and acute hypocalcaemia.

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