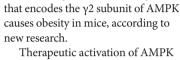


Consequences of AMPK activation

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...human carriers of the homologous mutation ... also exhibit increased adiposity..._



An activating mutation in the gene

has been proposed as a strategy to treat systemic metabolic diseases. As such, a team of researchers led by Arash Yavari and Houman Ashrafian decided to investigate the long-term consequences of AMPK activation.

To create a mouse model of increased AMPK activation, the team introduced an Arg299Gln mutation



into *Prkag2* (which encodes the murine γ 2 subunit); the resulting mice were termed R299Q γ 2 mice. The γ 2-specific AMPK activity of these mice was almost three times greater than that of wild-type mice.

At 40 weeks old, homozygous R299Q γ 2 mice had greater fat mass and frank hepatic steatosis compared with wild-type mice, as well as an increase in plasma levels of proinflammatory cytokines. These mice also had glucose intolerance and reduced insulin sensitivity, which are hallmarks of obesity.

Pair-feeding experiments with R299Q γ 2 and wild-type mice revealed that hyperphagia was the main contributor to the obesity of R299Q γ 2 mice. Further investigation demonstrated that the hyperphagia of these mice was dependent on increased ghrelin receptor signalling, which lowered the threshold for feeding.

Mice carrying this mutation also had impaired β -cell function, with reduced glucose-stimulated insulin secretion. The researchers showed that key functional islet genes, including those that encode insulin and glucokinase (*Ins1*, *Ins2* and Gck), were downregulated in islets from R299Q $\gamma 2$ mice, while several genes whose expression is normally selectively repressed in mature β cells were upregulated.

Importantly, heterozygous human carriers of the homologous mutation (an Arg302Gln missense mutation in *PRKAG2*) also exhibited increased adiposity, an increase in plasma markers of steatosis and reduced basal β -cell function with elevated HbA₁e.

"Our findings led us to conclude that long-term AMPK activation throughout all tissues can exert adverse metabolic consequences (particularly increased appetite and reduced β -cell function), which we suggest should be taken into account in pharmacological approaches that seek to chronically activate AMPK systemically," conclude Yavari and Ashrafian. "Nonspecific, generalized long-term AMPK activation, without reference to subunit composition or individual tissue effects, might result in harm rather than benefit."

Claire Greenhill

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