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BASIC RESEARCH

New metformin mechanism elucidated *in vitro* and *in vivo*

Results of a new study published in *Nature* shed light on the mechanism of action of metformin, one of the most widely used drugs for the treatment of type 2 diabetes mellitus.

When 2.5 years ago metformin was shown to lower glucose production in murine livers genetically modified to lack AMP-activated protein kinase (AMPK), the logical question to ask was: if metformin doesn't work through AMPK, how does it work? Among the people who asked themselves this question was Morris J. Birnbaum, Professor of Medicine at the University of Pennsylvania and senior investigator of the study. "No one had been looking at glucagon signalling, even though abnormal glucagon levels as a cause of diabetic hyperglycaemia had been receiving a lot of attention," remembers Birnbaum. In a first experiment, Birnbaum and co-workers added metformin to glucagon-treated hepatocytes and found that the rise in cAMP levels was completely inhibited, setting the stage for their recently published findings.

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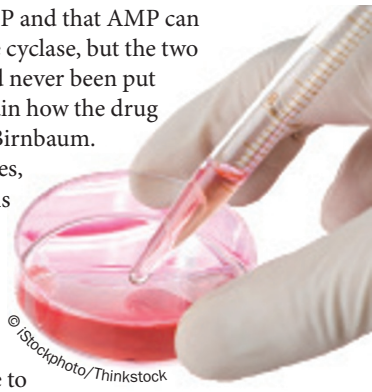
By employing a combination of genetic and biochemical approaches, both *in vitro* using isolated murine hepatocytes and *in vivo* in mice, Birnbaum's team found that metformin blocks the glucagon-dependent hepatic increase in cAMP. "This pathway is the major glucagon signalling pathway and is well-recognized to be essential to the increase in glucose output from the liver," explains Birnbaum. Metformin induces the accumulation of AMP, which in turn inhibits the integral membrane protein adenylate cyclase, reduces levels of cAMP and protein kinase A (PKA) activity and abrogates phosphorylation of critical protein targets of PKA. As a result, glucagon-dependent glucose output from murine hepatocytes is suppressed.

Most of the individual aspects of the study were already known; however, a coherent link between these findings had been lacking. "For example, it was known that metformin increases intracellular AMP and that AMP can inhibit adenylate cyclase, but the two observations had never been put together to explain how the drug works," reflects Birnbaum.



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In future studies, Birnbaum and his team hope to develop small molecules that bind the AMP binding site on adenylate cyclase to replicate the effects of metformin on glucose output. Moreover, high doses of metformin seem to act via a different mechanism, which the researchers hope to unravel.

Taken together, the results by Birnbaum and colleagues pave the way for new strategies to develop drugs that target type 2 diabetes mellitus.

Linda Koch

Original article Miller, R. A. *et al.* Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. *Nature* doi:10.1038/nature11808