Metal binding important for metformin action

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(HealthDay) -- The ability of metformin to bind mitochondrial copper may be essential to its mechanism of action, according to a study published online April 9 in *Diabetes*.

Noting that the target of metformin is unclear but most evidence has shown that the drug binds to metal ions, most stably to copper, rather than protein targets, Lisa Logie, Ph.D., from the University of Dundee in the United Kingdom, and colleagues interfered with the ability of metformin to bind copper and examined the impact on cellular responses.

The researchers found that copper sequestration interfered with the

known effects of metformin on AMP-activated protein kinase (AMPK)-dependent signaling and S6 protein phosphorylation, which were regulated independently. The metformin-copper interaction was stabilized by extensive pi-electron delocalization, which allowed regulation of AMPK, production of glucose, gluconeogenic gene expression, mitochondrial respiration, and mitochondrial copper binding. In contrast, direct modification of the metal-liganding groups of the biguanide structure prevented regulation of S6 phosphorylation. Further studies showed that pioglitazone also targeted mitochondrial copper.

"In summary, this study indicates that effects of metformin and related compounds on cell responses depend on their ability to interact with copper," Logie and colleagues conclude. "More broadly, our results suggest that the number of targets for drug discovery could be widened not only by investigating nonprotein targets such as copper, but also by considering the role of metal-induced effects on chemical bonding and conformational geometries of drug structures."

More information: Abstract
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