Molecular features of biguanides required for targeting of mitochondrial respiratory complex

11 August 2016

The biguanides are a family of drugs with diverse clinical applications. Metformin, a widely used anti-hyperglycemic biguanide, suppresses mitochondrial respiration by inhibiting respiratory complex I. Phenformin, a related anti-hyperglycemic biguanide, also inhibits respiration, but proguanil, which is widely used for the prevention of malaria, does not. The molecular structures of phenformin and proguanil are closely related and both inhibit isolated complex I. Proguanil does not inhibit respiration in cells and mitochondria because it is unable to access complex I. The molecular features that determine which biguanides accumulate in mitochondria, enabling them to inhibit complex I in vivo, are not known.

Here, a family of seven biguanides are used to reveal the molecular features that determine why phenformin enters mitochondria and inhibits respiration whereas proguanil does not. All seven biguanides inhibit isolated complex I, but only four of them inhibit respiration in cells and mitochondria. Direct conjugation of a phenyl group and bis-substitution of the biguanide moiety prevent uptake into mitochondria, irrespective of the compound hydrophobicity. This high selectivity suggests that biguanide uptake into mitochondria is protein mediated, and is not by passive diffusion. Only those biguanides that enter mitochondria and inhibit complex I activate AMP kinase, strengthening links between complex I and the downstream effects of biguanide treatments.

Biguanides inhibit mitochondrial complex I, but specific molecular features control the uptake of substituted biguanides into mitochondria, so only some biguanides inhibit mitochondrial respiration in vivo. Biguanides with restricted intracellular access may be used to determine physiologically relevant targets of biguanide action, and for the rational design of substituted biguanides for diverse clinical applications.

More information: Hannah R. Bridges et al. Molecular features of biguanides required for targeting of mitochondrial respiratory complex I and activation of AMP-kinase, *BMC Biology* (2016). DOI: 10.1186/s12915-016-0287-9

Provided by MRC Mitochondrial Biology Unit