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Type 2 diabetes and development of cardiovascular complications: A role of reactive oxygen species

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Type 2 diabetes is one of the major causes of cardiovascular disease. Insulin stimulates the generation of anti-atherosclerotic signaling molecule like Nitric Oxide (NO). The effects of increasing or decreasing insulin sensitivity, specifically on the endothelium due to the bioavailability of NO and vascular function, has not been widely investigated. We studied different models of insulin sensitivity and its effects in mediating atherosclerosis and cardiovascular complications. Different experimental models of insulin resistance at a whole-body level and specific to the endothelium demonstrated that insulin resistance eventually leads to an increase in generation of reactive oxygen species and accelerated atherosclerosis via the insulin receptor signaling pathways and these subjected mice have also demonstrated impaired acetylcholine-induced aortic relaxation. This impairment could be reversed by NADPH oxidase inhibitors, suggesting a role of reactive oxygen species in mediating insulin resistance and endothelial dysfunction.

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Repurposing drugs as a new approach for the treatment of type 2 diabetes

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Diabetes is one of the fastest growing diseases worldwide afflicting approximately 380 million people, primarily due to a dramatic increase in type 2 diabetes. Despite major investment by pharmaceutical companies in conventional drug discovery pipelines, development of new drugs has failed to keep up with the increasing incidence of type 2 diabetes. Drug repurposing, is the process in which the existing drugs are applied to a new indication and it is gaining momentum as a successful approach to overcome the bottlenecks commonly encountered with conventional approaches. Repurposing of drugs takes advantage of available information on the molecular pharmacology of clinical agents, to drastically shorten the drug development timelines. This talk will share our recent experience in repurposing existing drugs by targeting fatty acid oxidation (energy expenditure), *de novo* lipogenesis, mitochondrial metabolism, AMPK, CaMKKβ, Foxo1, ER stress, HSP72 and autophagy. The repurposed drugs in our laboratory include beberines (Diabetes 57:1414, 2008), triterpenpoids (*Chem Biol* 15:263, 2008; *PlosOne* 9:e10723, 2014), rutaecarpines (ACS *Chem Biol* 8:2301, 2013; *J Med Chem* 58:9395, 2015) matrine (Bri J Pharmacol 172:4303, 2015; BBA 1852:156, 2015). As well as revealing the new cellular targets for re-evaluation of the molecular mode of action for the treatment of diabetes, this presentation will also discuss relevant cell (*Biochem Pharmacol* 84: 830, 2012) and animal (*PlosOne* 7: e42115, 2012) models used in our studies in the screening process for this strategy.

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