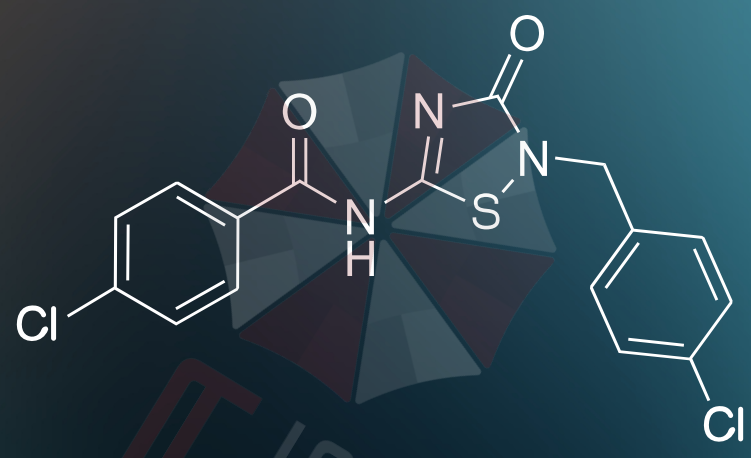


O304 As a Dual AMPK Activator and Exercise Mimetic: Preclinical and Clinical Insights

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History

O304 was first described in the scientific literature in 2018 by a group working in the Swedish University in Umea.[1] However, press reports from 2016 already mention the compound, hence it was likely discovered in the early 2010`s. Later, the company Betagenon AB has filed a patent application for a new betagenon formulation (WO2021074646A1). This is likely due to the fact that the structure had already been published in 2018 and was hence not able to be patented.

Phase 2 trials of O304 were already announced in 2016, however results have never been published.

In 2020, news about a new trial with O304 in combination with the SGLT-2 inhibitor Dapagliflozin were announced. However, results from this study have not been published either.

Mechanism of Action

O304 activates the enzyme AMP activated protein kinase (AMPK). This enzyme is a regulator of energy homeostasis in many cells and is physiologically activated in response to an energy shortage imposed by physical activity and/or caloric restriction. By binding directly to AMPK and enhancing its activity, O304 increases glucose uptake in skeletal muscle and improves mitochondrial function, thereby promoting efficient energy utilization. Unlike indirect AMPK activators such as metformin, O304 does not rely on cellular stress or inhibition of mitochondrial respiration to activate the pathway, which reduces the risk of off-target effects.

Preclinical Trials

Like physical exercise, O304 activated AMPK in the heart, increased cardiac glucose uptake, reduced cardiac glycogen levels, and improved left ventricular stroke volume in mice, but it did not increase heart weight in mice or rats. O304, which - in diet-induced obese mice - increased glucose uptake in skeletal muscle, reduced pancreatic β cell stress. It does also increase glucose uptake in skeletal muscle cells.[1]

In another study, the authors showed that O304 prevented and reverted age- associated hyperinsulinemia and insulin resistance, and improved cardiac function and exercise capacity in aged mice. These results provide preclinical evidence that O304 mimics the beneficial effects of exercise. Thus, as an exercise mimetic in clinical development, AMPK activator O304 holds great potential to mitigate metabolic dysfunction, and to improve cardiac function and exercise

capacity, and hence quality of life in aged human individuals as well. [2]

Another study in diabetic mice demonstrated that O304 stimulates insulin independent glucose uptake and utilization in skeletal muscle and heart in vivo, while preventing glycogen accumulation. The study also interestingly showed that O304 acts as a mitochondrial uncoupler, i.e., generates a metabolic demand. O304 averts gene expression changes associated with metabolic inflexibility in skeletal muscle and heart of diabetic mice and reverts diabetic heart disease. In Type 2 diabetic mice O304 preserves β-cell function by preventing decline in insulin secretion, β-cell mass, and pancreatic insulin content. Thus, as a dual AMPK activator and mitochondrial uncoupler O304 mitigates two central defects of type 2 diabetes; impaired glucose uptake/utilization and β-cell failure, which today lack effective treatment.[3]

In the kidney, renal tubular cells possess high abundance of mitochondria to meet the high energy consumption. AMPK also plays central role in maintaining energy homeostasis and mitochondrial homeostasis in these cells. Besides that, AMPK also commands autophagy, a clearing and recycling process to maintain cellular homeostasis. However, the effect of AMPK activators on kidney aging has not been fully elucidated. In another preclinical trial of O304 in naturally aging mice and D-Galactose (D-Gal)-treated renal tubular cell culture. The results showed that O304 beneficially protects against cellular aging and aged-related fibrosis in kidneys. Also, O304 restored energy metabolism, promoted autophagy and preserved mitochondrial homeostasis. Transcriptomic sequencing also proved that O304 induced fatty acid metabolism, mitochondrial biogenesis and ATP process, and downregulated cell aging, DNA damage response and collagen organization. All these results suggest that O304 has a strong potential to retard aged kidney injury through regulating AMPK-induced multiple pathways. [4]

Another potential application of O304 was discovered to be the prevention of aortic aneurisms. During aneurism development, vascular muscle cells transition from the contractile to the proliferative phenotype, a process that has previously been associated with AMPK pathway inhibition. O304, activated the AMPK pathway, preventing the muscle cells from phenotypic switching and inhibited aneurism formation in mice.[5]

Interestingly, O304 also seem to have potential application in back pain caused by intervertebral dis herniation.[6]

Clinical Trials

In the initial study from Umea university, a clinical study in human patients was performed. O304 reduced fasting plasma glucose and blood pressure and increases microvascular perfusion in type 2 diabetes patients on Metformin. The reduction in plasma glucose at day 28 compared with day 1 was -0.10 mM in the placebo group and -0.60 mM in the O304 group.[1]

Conclusion

O304 showed a variety of highly promising effects in preclinical trials and one clinical trial. It is hence unclear why no patent application has been handed in the early days of its discovery. This may be due to the fact that most of the preclinical trials have not been performed until after 2020, when a patent application was not possible anymore for the compound since it had already been published in 2018. Another reason may be that Betagenon AB did not find the compound interesting or problems with the regulatory bodies in the background arose.

Nerveless, O304 mimics the metabolic effects, it increases energy demand and improves skeletal muscle glucose metabolisation. It could be compared to an oral exercise pill, which is a highly sought after class of compound in medical sciences.

There is no data on the pharmacokinetics or toxicity of the chemical, which may also be a reason for the slow development of O304.

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