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Repurposing soluble guanylate cyclase stimulators from one to another isoform within the ROCG signalling module

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Abstract

Currently, most disease treatments are symptom- based without any mechanistic basis, leading to unmet medical need and high numbers needed to treat. Identifying the underlying disease mechanisms is key for precise treatment and drug repurposing. One example is an impaired signalling network related to reactive oxygen species (ROS) involvement with cGMP signalling (the ROCG disease module). This disease module is relevant for a heterogenous cluster of neurological, metabolic, and pulmonary disease phenotypes [1]. ROS formation by NADPH oxidases (NOX) can affect the ROCG module in several ways: (i) scavenging of NO and further increase of ROS production, (ii) NO synthase (NOS) uncoupling, and (iii) formation of insensitive to NO oxidised/heme-free soluble guanylate cyclase (sGC)[2, 3]. By targeting different parts of this pathway with a network pharmacology approach, we could restore the physiological state in a highly synergistic manner. Such drugs are also already available in the clinic. For example, Riociguat is registered for pulmonary arterial hypertension and belongs to the so-called sGC stimulators (sGCs) which are thought to act exclusively on NO-sensitive sGC[3]. Here, we show that sGCs are also able to stimulate the oxidised/heme-free form of sGC, the so-called apo-sGC. Moreover, we show that sGCs combined with sGC activators (registered as activators of apo-sGC) yield additive or supra-additive effects on apo-sGC. This data suggests that sGCs can be repurposed for cases where apo-sGC is the primary form of the enzyme, such as overproduction of reactive oxygen species. A promising example is acute ischemic stroke[1]. For this indication, three drugs targeting the ROCG network are being repurposed: (i) riociguat, targeting almost exclusively apo-sGC, (ii) propylthiouracil, registered as an antithyroid drug but also acting as a NOS inhibitor[4], and (iii) perphenazine, an antipsychotic drug acting as an NOX inhibitor[5] (REPO-STROKE II, EudraCT no. 2019– 000474-31). In conclusion, our data suggest that drug repurposing for different target proteins and indications can be easily translated to direct patient benefit.

Keywords

Drug repurposing, network pharmacology, sGC stimulators, stroke

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