Guaiacol – a novel drug candidate for treating Adult Polyglucosan Body Disease

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Background: APBD is caused by intracellular accumulation of insoluble inclusion bodies called polyglucosans, formed as a result of glycogen branching enzyme (GBE) deficiency. To identify drug candidates for APBD, we used high throughput screening (HTS) of FDA approved drugs, a promising strategy for drug repurposing. One of the discovered candidates was Guaiacol, a flavorant originally prescribed for relieving cough and reflux.
Methods: We performed HTS in fibroblasts from *Gbe1*$^{ys/ys}$ (APBD modeling) mice and from patients using the LOC 1100 FDA approved compound library. The HTS readout was diastase resistant, periodic-acid Schiff reagent positive, polyglucosans. The effect of Guaiacol on glycogen synthase (GYS1) activity was tested by an established biochemical assay, or by on gel assay of a glycogenin-GYS1 chimera, where the effect of Guaiacol on glycogenin activity was excluded by mass-spectrometry.
Results: Consistent with the Guaiacol-mediated increase in inhibitory GYS1 phosphorylation in mice, the drug inhibited both basal and glucose-6-phosphate stimulated GYS1 activity in both purified enzyme and APBD patients' cell lysates. Furthermore, Guaiacol also increased phosphorylation of the master activator of catabolism, AMP-dependent kinase. Guaiacol also restored the significantly shorter lifespan of *Gbe1*$^{ys/ys}$ mice to normal levels, and caused no adverse effects except slightly reduced glucose tolerance. In addition, Guaiacol reduced liver polyglucosan and glycogen levels, and corrected penile prolapse in the aged *Gbe1*$^{ys/ys}$ male mice.
Conclusions: Restoration of the reduced life span of APBD modeling mice by Guaiacol as well as its additional effects are encouraging. Together with the lack of observable significant side effects, our results form the basis for future clinical trial. Interestingly, despite its curative effect, the only organ in which Guaiacol reduced polyglucosans was the liver, which apparently is not pertinent to neurological damage in APBD.