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Old drugs open new horizons for the treatment of neuropathic pain

Aim: Increased tetrahydrobiopterin (BH4) generated in injured sensory neurons contributes to increased pain sensitivity and its persistence. Polymorphisms in the GTP cyclohydrolase 1 (*GCH1*) gene, a rate-limiting enzyme in the de novo BH4 synthetic pathway, have been associated with chronic pain severity. This study aimed to investigate the regulatory mechanisms of *Gch1* expression upon nerve injury and explore whether this could be modulated as an analgesic therapeutic intervention.
Methods: In order to identify and characterize several hits that reduce or enhance GCH1, the authors screened over 1000 target-annotated and U.S. Food and Drug Administration (FDA)–approved drugs for regulating expression of GCH1 in a model of axotomized (injured) mouse primary DRGs isolated from Gch1-GFP transgenic reporter mice. The authors also performed a computational STITCH (Search tool for interactions of chemicals) analysis of the validated hits to map protein and pathway targets. Eventually, the authors confirmed the utility of the approach by testing the top candidates in vitro and in vivo in a neuropathic spared nerve injury (SNI) model.
Results: From this approach, the authors uncovered relevant pathways that regulate *Gch1* expression in sensory neurons. They screened multiple FDA-approved compounds and showed that the antipsychotic fluphenazine hydrochloride reduced GCH1 expression substantially and had analgesic effects in a neuropathic pain model in rodents. Among the hits, the authors also reported that EGFR/KRAS pathway blockers similarly reduced pain sensitivity by decreasing GCH1 expression and the levels of BH4. EGFR and KRAS are the two most frequently mutated genes in lung cancer. The authors wanted to push this study further and explore whether the GCH1/BH4 axis also holds importance for KRAS-dependent cancer development. The authors demonstrated that GCH1/BH4 pathway blockage in a mouse model of KRAS-driven lung cancer led to reduced tumor burden and increased survival rate among the mice.
Conclusions: This study shows that pharmacologic modulation of GCH1 expression and BH4 could be used to develop pharmacological treatments to alleviate pain and identified a critical role for EGFR-regulated GCH1/BH4 expression in neuropathic pain and cancer in rodents.

Comments. The authors of this study had previously shown that sensory neurons produce a specific metabolite, BH4, which drives chronic pain, and that the concentrations of BH4 correlated very well with the pain intensity. The current study demonstrated in an original approach, the value of a phenotypic screen with an annotated drug library to identify existing drugs that may be repurposed for treating chronic pain. One drug identified by the screen was fluphenazine hydrochloride which demonstrated its effects in treating chronic pain by decreasing GCH1 expression and BH4 levels upon nerve injury in preclinical models. Additionally, multiple compounds targeting the EGFR pathway were among the most effective reducers of GCH1 expression. The screen uncovered a novel and unexpected common molecular therapeutic target for EGFR/KRAS-mediated pain perception and lung cancer via the GCH1/BH4 metabolic pathway, opening the door for multiple therapeutic opportunities. This study still needs to be further validated on other relevant mouse models of inflammatory and neuropathic pain as well as on human neuron cultures (e.g. induced pluripotent stem cell (iPSC)–derived human nociceptors) as a promising translational step from mouse studies to a human platform.

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Reference. Cronin SJF, Rao S, Tejada MA, Turnes BL, Licht-Mayer S, Omura T, Brenneis C, Jacobs E, Barrett L, Latremoliere A, Andrews N, Channon KM, Latini A, Arvanites AC, Davidow LS, Costigan M, Rubin LL, Penninger JM, Woolf CJ. Phenotypic drug screen uncovers the metabolic GCH1/BH4 pathway as key regulator of EGFR/KRAS-mediated neuropathic pain and lung cancer. Sci Transl Med. 2022 Aug 31;14(660):eabj1531. doi: 10.1126/scitranslmed.abj1531.
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