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Editorial comment

GTP-cyclohydrolase 1 genetics and tetrahydrobiopterin—Modulators of pain hypersensitivity? An interesting target for understanding the process of pain vulnerability and a potential treatment option for pain

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In this issue of *Scandinavian Journal of Pain*, Nasser and Birk Möller present a topical review on the role of the guanosine triphosphate cyclohydrolase 1 (GCH1) genetics and the down-stream effects of tetrahydrobiopterin (BH4) in the pathophysiology of pain [1]. The review is based on the findings presented in Dr. Nasser's recent PhD dissertation, titled "*Involvement of the GCH1 gene and the cofactor tetrahydrobiopterin in pain – a comparative study in mice and man*" (University of Copenhagen 2013).

1. Why does acute pain become chronic in some patients?

In patients undergoing the same surgical procedure, it has been shown that about 80% are pain free when followed up after some years, but around 20% still suffer from varying degrees of persistent pain, in some cases severe pain. Is this long term outcome concerning chronic pain due to a genetic disposition? Many research groups are at present investigating this question, and a multitude of candidate genes predisposing for vulnerability to chronic pain are suggested [2].

2. In search for a genetic explanation for pain vulnerability – the role of GCH1 and BH4

The BH4 story in the pain field was kindled by an important publication by Tegeder et al. [3], showing that a certain GCH1 gene haplotype seemed to be "pain protective". This interesting result has been replicated in some further studies, but not in others (see review in ref. [1]). Thus, we need to know more, in order to understand the complex interplay between GCH1, BH4 and nociception/pain sensitivity. Here Nasser and Birk Möller add some new information to this important issue in pain research.

BH4 is a co-factor involved in the regulation of the synthesis of nitric oxide and monoamines, both of importance for the processing of pain. The GCH 1 gene is coding for the enzyme GTP cyclohydrolase 1 that is critical for the biosynthesis of BH4. Certain GCH1 mutations seem to be "pain protective". They are present in about 15% of the general human population, are according to some studies [3] leading to a decrease in the GCH1 enzyme activity, resulting in lower synthesis of BH4.

3. Pain reactions in humans suffering from BH4 deficiency

In this publication the authors present unique data from their pain studies in volunteer patients suffering from the very uncommon disease DOPA-responsive dystonia (DRD). These patients have mutation in the GCH 1 gene, leading to low levels of BH4. It seems like changes in the BH4 concentration are not affecting all pain types alike. Preliminary results indicate that the DRD patients have the same pain thresholds for acute mechanical or heat pain stimuli as healthy controls, while the DRD group showed signs of less pain sensitivity in models including chemical sensitization/inflammation.

4. BH4 seems more important for pain due to inflammation and "sensitization"

This finding is supported by experimental studies, where Nasser and Möller Birk show that in hyperphenylalaninemia-1 mice, considered to represent a model of human DRD, having low GCH 1 activity and BH4 synthesis. The mutant mice showed no change in their pain-like reaction following "physiological" mechanical and heat stimuli, but after induction of inflammation inducing hypersensitivity, the pain reactions were decreased, just as seen in the DRD patients. The interpretation is that the pain protective GCH1 haplotype with low BH4 levels, are mainly confined to pain sensitization models. It is also shown that pharmacological inhibition of GCH1 enzyme activity causes antinociception in rat models of neuropathic and inflammatory pain.

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5. Sulfasalazin- and old drug with a potential for analgesia?

Another potential target to achieve reduction of BH4 levels is by competitive inhibition of the last synthesis step by blocking the enzyme sepiapterin reductase (SR). One experimental drug with this capacity, N-acetylserotonin attenuated inflammatory and neuropathic pain behaviours in rats [3]. The drug sulfasalazine, already for a long time used in humans to treat rheumatoid arthritis and colitis, is also an inhibitor of SR. The role of sulfasalazine as a drug with analgesic potential is further supported by a recent publication, where sulfasalazine was shown to decreased pain behaviour in a bone pain cancer model in rats. However, the main explanation to the effect seen in that study did not involve the target BH4. Instead sulfasalazine was used in its capacity to produce a glutamate release inhibition from breast cancer cells [4]. Thus, it seems like sulfasalazine may have at least two modes of action to produce analgesia. With this background, the interesting main hypothesis raised by Nasser and Birk Möller, whether BH4 reduction could give an analgesic effect, actually may be tested in humans, provided the necessary formal approvals are given.

John W. Severinghaus, a pioneer in anaesthesiology/respiratory research on the measurement of blood gases, once stated his view on research, saying: “by knowing the process, better the art” [5]: I think he meant that the more in detail we know about what is going on in a physiological process, the better we can find solutions that in the longer perspective may help our patients to better treatment.

Applied in the field of pain research, I believe the results presented here really contribute to this goal. The findings by Nasser and Möller Birk represent a fine example of translational pain research.

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None declared.

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