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Research Report

The H_2S-producing enzyme CSE is dispensable for the processing of inflammatory and neuropathic pain

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ABSTRACT

Accumulating lines of evidence indicate that hydrogen sulfide (H_2S) contributes to the processing of chronic pain. However, the sources of H_2S production in the nociceptive system are poorly understood. Here we investigated the expression of the H_2S releasing enzyme cystathionine γ-lyase (CSE) in the nociceptive system and characterized its role in chronic pain signaling using CSE deficient mice. We show that paw inflammation and peripheral nerve injury led to upregulation of CSE expression in dorsal root ganglia. However, conditional knockout mice lacking CSE in sensory neurons as well as global CSE knockout mice demonstrated normal pain behaviors in inflammatory and neuropathic pain models as compared to WT littermates. Thus, our results suggest that CSE is not critically involved in chronic pain signaling in mice and that sources different from CSE mediate the pain relevant effects of H_2S.

Abbreviations: BCA, β-cyanoalanine; CAT, cysteine aminotransferase; CBS, cystathione β-synthase; CSE, cystathionine γ-lyase; DRGs, dorsal root ganglia; H_2S, hydrogen sulfide; K_{ATP}, ATP-sensitive K^+; LPS, lipopolysaccharides; MPST, 3-mercaptopyruvate sulfurtransferase; PGE_2, prostaglandin E2; PLP, pyridoxal-5′-phosphate; PPG, DL-propargylglycine; SNI, spared nerve injury; TRP, transient receptor potential; WT, wildtype

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1. Introduction

Chronic pain in response to tissue damage (inflammatory pain) or nerve injury (neuropathic pain) is a major clinical health problem, affecting up to 30% of adults worldwide. As currently available treatments are only partially susceptible, it is important to elucidate molecular mechanisms of pain signaling in detail to obtain new insights in potential future therapies (Basbaum et al., 2009; Ji et al., 2014; Johannes et al., 2010). Recent studies suggested the contribution of reactive oxygen species and redox-active gasotransmitters such as hydrogen sulfide (H_2S) to pain signaling (Kallenborn-Gerhardt et al., 2013b; Salvemini et al., 2011; Schmidtko et al., 2009). H_2S is a small gas molecule that is thought to travel through cellular membranes and to act on a variety of cellular targets (Olson, 2012; Wallace and Wang, 2015; Wang et al., 2014; Wang, 2002). Several studies pointed to a contribution of H_2S to pain processing, however pro- as well as antinociceptive effects have been described so far (for review see Smith (2009), Distrutti (2011) and Terada and Kawabata, (2015)). For example, carrageenan injection into a hindpaw induces local H_2S formation (Bhatia et al., 2005) and intraplantar injection of the H_2S donors NaHS, Na_2S or L-cysteine induces hyperalgesia (Kawabata et al., 2007; Sekiguchi et al., 2014). In a model of irritable bowel syndrome intracolonic injection of NaHS led to increased pain responses (Matsunami et al., 2009). Moreover, several studies demonstrated direct stimulating effects of NaHS on the activity of dorsal root ganglia (DRG) neurons (Andersson et al., 2012; Hu et al., 2013; Matsunami et al., 2009; Xu et al., 2009). On the other hand anti-nociceptive effects of H_2S have also been suggested. H_2S donors attenuated leukocyte adherence and edema formation in inflammatory models (Andruski et al., 2008; Zanardo et al., 2006). NaHS may dose-dependently reduce LPS- and PGE_2-induced hyperalgesia and zymosan-induced articular pain responses (Cunha et al., 2008), and systemic administration of NaHS decreased nociceptive responses in a model of irritable bowel syndrome (Distrutti et al., 2006). Furthermore, it has been shown that the H_2S donor Na_2S activates the μ-opioid receptor MOR (Distrutti et al., 2010). Therefore, it has been suggested that H_2S similar to nitric oxide may display a dual role in the signaling of chronic pain processes. However, the sources of H_2S production are so far only poorly understood.

In general H_2S is enzymatically formed from cysteine by (1) cystathionine γ-lyase (CSE), (2) cystathione β-synthase (CBS) or (3) 3-mercaptopyruvate sulfurtransferase (MPST) in combination with cysteine aminotransferase (CAT). While the expression of CBS is enriched in the brain, CSE has been found to be the predominant H_2S releasing enzyme in peripheral tissues (Kimura, 2013; Wang et al., 2014). CSE expression was detected in the spinal cord and DRGs (Distrutti et al., 2006; Takahashi et al., 2010; Wang et al., 2012) and various studies using CSE inhibitors in different pain models point to a contribution of this enzyme to chronic pain processing (Donatti et al., 2014; Kawabata et al., 2007; Lee et al., 2008; Matsunami et al., 2012; Velasco-Xolalpa et al.,

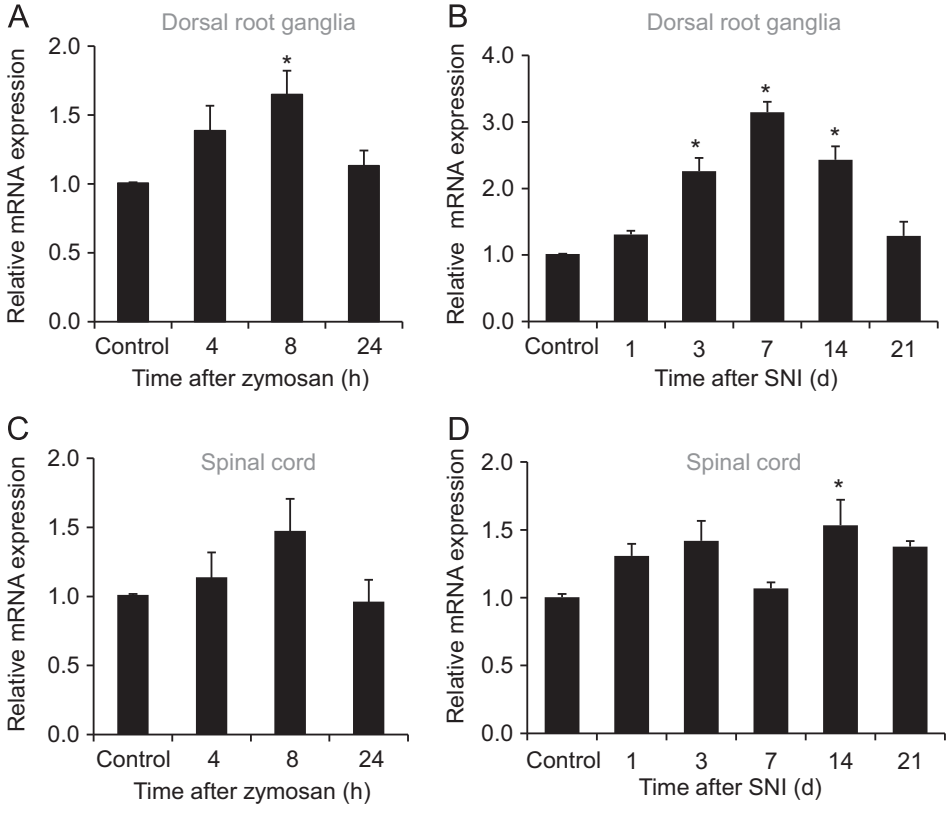

Fig. 1 – CSE expression in chronic pain models. CSE mRNA levels are significantly elevated in DRGs after zymosan injection into one hindpaw (A) and after spared nerve injury (B). In the spinal cord CSE is not significantly induced in the zymosan model (C) but 14 d after SNI surgery (D). $n=3–5$, $p<0.05$.