Role of quinone reductase 2 (QR2) in a rat model of inflammatory pain

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In the last two decades, animal models have become important tools in understanding and treating pain, and in predicting analgesic efficacy, which can lead to the development of clinical drugs. The animal models have also encouraged multidisciplinary analysis in the field of pain studies (Gigliuto et al., 2014). Inflammation is a key component of pain, as highlighted by the effectiveness of the nonsteroidal anti-inflammatory agents in acute inflammatory pain (Wang et al., 2004). Recent studies suggest that free radicals and reactive species are significantly involved in a variety of pain conditions, including neuropathic and inflammatory pain. There is a large amount of evidence showing that reactive oxygen species production ($^{-}O_2$, NO, H_2O_2 and ^{-}OH) occurs at the site of inflammation and contributes to tissue damage. Melatonin is a hormone synthesized principally in the pineal gland that has been classically associated with endocrine actions. However, several lines of evidence suggest that melatonin plays a role in pain modulation. Recently, melatonin induced-antinociception has been evidenced during neuropathic pain states. This effect agrees with the localization of melatonin receptors in thalamus, hypothalamus, dorsal horn of the spinal cord, spinal trigeminal tract, and trigeminal nucleus (Ambriz-Tututi et al., 2009). The effects of melatonin result from activation of MT1, MT2 and MT3 melatonin receptors. Quinone reductase 2 (QR2) has been identified as the melatonin MT3 receptor located in the cytoplasm which may mediate some of the antioxidant activities of melatonin.

Melatonin administration demonstrated antinociceptive effect also during acute inflammatory pain. Indeed, melatonin administration was able to inhibit both inflammation and hyperalgesia induced by subplantar injection of carrageenan in rats.

According to this knowledge, here we show that melatonin administration is able to inhibit carrageenan-evoked thermal hyperalgesia in a dose-dependent manner and that melatonin administration is able to induce a change in QR2 expression level in the rat spinal cords.

These results suggest that antinociceptive melatonin effect is mediated by the MT3 receptor at spinal level. Therefore QR2 melatonin receptor constitutes attractive targets for developing analgesic drugs, and its activation may prove to be a useful strategy to generate analgesics with a novel mechanism of action.

Gigliuto et al. (2014). *Journal of Pain Research.* 7, 227–236.
Wang et al. (2004). *JPET.* 309, 869–878.
Ambriz-Tututi et al. (2009). *Life Sciences.* 84, 489–498.