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COMMENTARY

Taking the sting out of pain

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While the role of the brain kallikrein-kinin system in the development of various pathological processes, such as oedema formation following brain injury or induction of central hypertonia has generated major interest, the possible role of this system in nociceptive processing has received little attention. In their present paper, Mortari *et al.* (2007) show that bradykinin B2 receptor activation in the brain by the bradykinin analogue, Thr[6]-bradykinin, isolated from the venom of the social wasp, *Polybia occidentalis* potently reduces acute, noxious heat-evoked reflex responses in naive rats. The unknown underlying mechanism of this powerful antinociceptive effect reminds us that the supraspinal antinociceptive system is still a ''black box'' in many aspects and awaits thorough investigation.
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Abbreviations: BK, bradykinin; LC, locus coeruleus; PAG, periaqueductal grey; Thr[6]-BK, Thr[6]-bradykinin

Mortari *et al*. (2007) report in this issue that injection of Thr[6]-bradykinin (Thr[6]-BK), which is the active peptide in the venom of the social wasp, *Polybia occidentalis*, into the lateral ventricle of naive rats reduces noxious heat-evoked responses both in tail-flick and hot plate tests. The authors also report that the Thr[6]-BK-evoked antinociceptive effect is mediated through the bradykinin (BK) B2 receptor, and it was superior to, or comparable with the antinociceptive effects produced by intracerebroventricular injection of BK or morphine, respectively. The powerful antinociceptive effect of Thr[6]-BK, and in fact BK itself, could be surprising to many, because BK and its analogues are most often associated with peripheral events, such as inflammation and damage of the peripheral tissues, and the induction of pain through the activation of a sub-population of nociceptive primary sensory neurons (Walker *et al*., 1995; Raidoo and Bhoola, 1998; Moreau *et al*., 2005). The finding that Thr[6]-BK and BK reduce noxious heat-evoked behavioural responses could even look controversial, because the pain sensation BK evokes in the periphery is heat hyperalgesia.

Members of the kallikrein–kinin system, including tissue kallikrein, the enzyme which cleaves BK analogues, BK itself, the BK B2 receptor and the kininases that hydrolyze kinins, have all been found in various areas of the brain, including the cortex, cerebellum, hypothalamus, brain stem and the pituitary gland (Raidoo and Bhoola, 1998; Chen *et al*., 2000; Moreau *et al*., 2005). Accordingly, BK and the B2 receptor have been implicated in a series of pathological processes, including the development of post-traumatic and inflammatory brain oedema, Alzheimer's disease and central hypertonia (Raidoo and Bhoola, 1998; Moreau *et al*., 2005). The effect of BK on nociceptive processing in the brain has, however, received little attention. Thus, the mechanism involved in the Thr[6]-BK-evoked antinociceptive effect remains elusive.

Mortari and her co-workers suggest that Thr[6]-BK produces antinociception by activating the descending adrenergic pathways through presynaptic B2 receptors. This hypothesis is based on earlier findings that BK injected into the locus coeruleus (LC) or the principal spinal trigeminal nucleus, which receives projection from the LC, produces powerful antinociception that is abolished when noradrenaline is depleted in the LC (Couto *et al*., 1998, 2006). However, other mechanisms should also be considered, because in addition to the LC, other brain regions, which are involved in nociceptive processing, and have been shown to respond to BK and/or express B2 receptors, could also be accessed easily by Thr[6]-BK from the lateral ventricle. For example, BK produces antinociception when injected into the periaqueductal grey (PAG), one of the main sites, which integrates the endogenous descending pain modulation (Burdin *et al*., 1992). The PAG-mediated effect could include neurons with perikarya located in the amygdala, because injection of the μ-opioid agonist, DAMGO, into the basolateral part of the amygdala that expresses B2 receptors in high density inhibits the tail-flick reflex through the PAG (Helmstetter *et al*., 1998; Chen *et al*., 2000), and easily accessible for drugs from the lateral ventricle. Alternatively, BK and its analogues could activate neurons indirectly, through inducing the release of substances from B2 receptor-expressing ependyma cells, oligodendrocytes or astrocytes (Raidoo and Bhoola, 1998; Chen *et al*., 1996).

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Regardless of the underlying mechanisms, findings by Mortari *et al*. (2007) and other authors show that the kallikrein–kinin system, particularly via the B2 receptor, is very much a part of the endogenous antinociceptive system. At this time, there are more questions than answers about this supraspinal pain control and it is too early to consider the exploitation of this system for pain control. First, we should elucidate whether the kallikrein–kinin system is able to reduce pathological pain sensations, such as heat/cold hyperalgesia and mechanical allodynia associated with acute and chronic diseases. Furthermore, we should identify the mechanism(s), through which the BK-evoked antinociceptive effect is produced. It is also essential to investigate the possibility of the release of any endogenous B2 receptor agonists, which could selectively activate B2 receptors in areas and nuclei involved in nociceptive processing, because B2 receptor activation is involved in a series of pathological events (Raidoo and Bhoola, 1998; Moreau *et al*., 2005). Nevertheless, the present and previous findings of Mortari *et al*., indicate that the reward might be worth the effort, because, while wasps buzzing over our heads are a nuisance, they could offer more than a sting.

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