Exploring the nociceptor basis of thermal hyperalgesia.

Hyperalgesia, also described as increased sensation of pain from already nociceptive stimuli, is a condition that can occur from an injury or from consumption of certain drugs like opioids[1]. These can lead to an increase in sensitivity or perception of intensity to painful stimuli due to a decrease in sensory threshold of nociceptors[2]. Hyperalgesia can come from chronic or persistent pain, in which the latter includes nociceptive and neuropathic pains. Nociceptive pains come from nociceptor activation through tissue damage leading to inflammation, and neuropathic pains come from injuries to peripheral or central nerves. Hyperalgesia can also cause spontaneously perceived pain[3]. There are three types of hyperalgesia: primary, which happens at the site of injury due to sensitization but may also be due to modified processing in the central nervous system (CNS); secondary, which happens around or away from the site of injury due to changes in sensory processing in the CNS; and referred, which also happens in the skin or at the surface, away from the affected tissue[2].

There are different types of nociceptors; mechanical, thermal, and polymodal. Silent nociceptors will be discussed later. Mechanical and thermal nociceptors are made of A-delta fibers with fast signal conduction, and polymodal nociceptors are made of C fibers which have slow signal conduction, and can be activated by mechanical, thermal, and chemical stimuli. These differences in signal conduction explain how, for example, thermal pain is felt very quickly through A-delta fibers, followed by a slower, duller pain from the polymodal nociceptors C fibers which are also activated from thermal nociceptive stimuli[3]. Additionally, modalities are differentiated through their distinctive labeled lines. The stronger the activation of these nociceptors, the more action potentials are discharged, hence the more intense the pain sensation is perceived[4].

In hyperalgesia, it is the sensitization of nociceptors and the resulting excitability changes of CNS neurons (also sensitized) caused from injury that are responsible for increased pain sensitivity. The injured tissue is more vulnerable, so the nociceptive system's adaptive response is to decrease the local nociceptive threshold to respond more easily to nociceptive stimulus and ensure better protection of the affected tissue. However, hyperalgesia can also be maladaptive and considered a disease; this can result from neuropathic pain as described earlier, and central sensitization[2]. For thermal hyperalgesia, the protein TRPV1, located in primary sensory neurons

within the nociceptive pathway, is responsible for pain perception from high heat, as well as capsaicin found in chilli peppers[5]. It is hence crucial for thermal hyperalgesia caused from tissue injury and will be discussed later[6].

The types of nociceptors involved in primary heat hyperalgesia are polymodal nociceptors as they are linked to C fibers. Increased C fiber activity was observed after a mild burn injury resulting in heat hyperalgesia due to decreased heat threshold and a bigger response from suprathreshold heat stimuli. However, A-delta thermal nociceptors can also play a role in primary heat hyperalgesia as they were found sensitized after a heat injury in glabrous skin of monkeys, though C fibers were not. It was concluded that the type of nociceptor sensitized in heat hyperalgesia depends on the skin type affected and the injury severity[7]. Additionally, silent nociceptors are a type of nociceptor not activated by painful stimulus but get activated from the inflammatory response following tissue injury as it heavily decreases their firing threshold. Silent nociceptors therefore contribute to central sensitization and secondary hyperalgesia[3]. IB4-binding nociceptors may also be involved in hyperalgesia and will be discussed next[8].

IB4-binding nociceptors in the sciatic nerve of rats are responsible for sensitivity to noxious stimuli and are therefore important for acute pain signalling. Their selective deletion resulted in increased thresholds for both thermal and mechanical nociceptive stimuli. Interestingly, the effects of their permanent deletion did not last as the thresholds returned to normal after 21 days due to compensation by changing the nociceptive stimuli processing to still protect the area from painful stimuli[8]. This ties back to hyperalgesia resulting from central sensitization, hence modified processing in the CNS which can be seen in both primary and secondary hyperalgesia. Another interesting molecular basis of changes in nociceptor is nerve growth factor (NGF) which, when antagonized, lead to a sustained thermal (and chemical) hypoalgesia, the opposite reaction to hyperalgesia. NGF is therefore necessary for maintaining the sensitivity of nociceptive sensory neurons. It may also be responsible for changes in the CNS processing of pain in hyperalgesia when upregulated. NGF antagonists can therefore be considered for hyperalgesia treatment and chronic pain in general[9]. Lastly, TRPV1 also acts on the sensitivity to painful heat stimuli as previously mentioned, it plays a part in thermal hyperalgesia as increasing its activity underlies the sensitization leading to it[6,10]. Some TRPV1 antagonists hence also have high value for potential treatment for thermal hyperalgesia[10].

Increasing TRPV1 activity in an environment without NGF activity can be prevented with an anti-NGF, however, anti-NGF cannot block TRPV1 induction in an environment with IB4-binding sensory neurons. This demonstrates that the NGF increase caused by inflammation facilitates the expression of TRPV1 only in specific types of neurons to cause thermal hyperalgesia[11].

One of the methodologies used to understand the molecular and cellular basis of hyperalgesia was the unilateral IB4-saporin injection. This injection is carried out in the sciatic nerve to destroy a specific subset of sensory neurons (IB4-binding neurons) and observe the response to noxious stimuli without them in order to understand their role in sensitivity to pain[8]. Another methodology used was the sequestration of endogenous NGF by administering trkA-IgG which is a protein designed to block its biological activity. The effects of this sequestration are then tested to understand the role NGF in relation to thermal nociception[9]. Both of these methods also allowed to understand how treatment can be developed against hyperalgesia. The last methodology discussed consisted of creating TRPV1 knockout mice and testing their reactions and sensitivity to different painful stimuli to understand which noxious modalities TRPV1 is responsible for *in vivo*[6].

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