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Review

Peripheral mechanisms of burn injury-associated pain

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ABSTRACT

It is estimated that burn injury affects about 1 in 3000 people annually world-wide. Burn injury induces severe pain, which is difficult to control in the great majority of cases making burn injury-associated pain a serious clinical challenge. In order to meet this clinical need, novel targets should be identified. Like pain developing in other peripheral pathologies, burn injury-associated pain is also initiated and maintained by signalling between the injured tissues and primary sensory fibres that supply those tissues. This signalling is underlain by the formation and accumulation of a mixture of agents at the site of the injury, some of which could be targets for intervention. However, at present the composition of this "burn injury tissue fluid" is incompletely established. Here, we summarise our current understanding of the composition of this burn injury tissue fluid and explore how already known agents in that tissue fluid may activate nociceptors to initiate and maintain pain associated with burn injury.

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1. Introduction

Pain resulting from burn injuries is one of the most excruciating pain sensations that can be experienced. It is estimated that 1 in 3000 people suffers burn injuries annually world-wide. According to WHO statistics, almost 11 million required medical attention due to the severity of their injuries in 2004 (WHO, 2008). Although, Europe has a lower incidence of burn injury than other areas in the world, annually 0.2–2.9/100,000 inhabitants suffer severe burn injury (Brusselaers et al., 2010). Improvements in resuscitation, wound care, critical illness support and infection control have improved the outcomes of burn injuries, and increased survival significantly (Brusselaers et al., 2005; DeSanti, 2005). Yet, pain in burn injury patients, both in the acute and chronic setting, is still a major clinical challenge and an unmet medical need (Carrougher et al., 2003; Dauber et al. 2002). Poorly treated pain in burn injury however, can lead to immense suffering, loss of engagement in treatment, development of chronic pain (Browne et al., 2011) and post traumatic stress disorder (Patterson et al., 2006). Further, the lack of appropriate pain control may significantly hamper successful functional recovery, which can lead to reduced integration into society (Esselman et al., 2001). Therefore, providing appropriate pain control following burn injury is of imperative importance.

The lack of appropriate pain control in burn-injured patients reflects our surprisingly limited understanding of the neuronal mechanisms involved in burn injury-associated pain. Understanding the signalling between the burned and subsequently inflamed tissues, and the sensory neurons that innervate those tissues, particularly at a cellular and molecular level therefore, must be

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one of the priorities in pain research. In this review, we will give an account on already known and putative signalling events occurring between burned tissues and primary sensory neurons, in the hope that we initiate further studies to elucidate peripheral mechanisms of burn injury-associated pain which will ultimately lead us to better pain management in these patients.

2. Pathology of burn injury

The aetiology of burn injury is diverse and it includes contacts with hot liquids, (scalds), various chemicals (chemical burn), strong electrical currents (electrical burn), flames or hot objects (contact burn). All tissues, which have some contact with the external environment, are susceptible to direct burn damage, including the skin, gastrointestinal and respiratory tracts. However, the majority of burn injuries are due to heat impact (Brusselaers et al., 2010) and affect the skin. Therefore, in this review we will concentrate on mechanisms involved in the development and maintenance of pain associated with heat-induced injury of the skin.

Although burn injury has a diverse aetiology, there is some consistency in the overall pathological process of burns to the skin and its subsequent impact on pain. The skin is a bilayer organ with both protective and immunological functions (DeSanti, 2005; Kao and Garner, 2000). It comprises of the outer epidermal layer, predominantly of keratinocytes, and the inner dermal layer. The dermis further divides into the superficial papillary dermis, and the deeper, reticular dermis. The papillary dermis has greater capacity to regenerate than the reticular dermis. Therefore, the depth of the injury to the skin determines healing and management (DeSanti, 2005; Kinsella and Rae, 1997). The depth of injury has also been used to classify or predict pain following burn injury (Kinsella and Rae, 1997; see Table 1).

The progression of burn injury involves initial tissue damage, inflammation and then healing and remodelling. Primary tissue damage occurs predominantly via thermal denaturing of proteins and loss of the plasma membrane integrity leading to cell death and the leakage of a series of agents (Evers et al., 2010; Fig. 1). Following the initial loss of tissues, there is an enormous inflammatory response (Allgower et al., 1995; Fig. 1). Locally this involves a prolonged influx of inflammatory cells that release various agents which, on the one hand, coordinate the action of immuno-competent cells, while on the other hand, act on sensory neurons inducing either direct activation or sensitisation (Fig. 1). The action of

Table 1
Correlation between depth of burn injury, pain and healing time.
Table is adapted from Evers 2010.

Depth	Layer of skin involved	Pain	Healing time
Superficial	Epidermis	– Moderate to severe pain	3–7 days
Superficial partial	Superficial papillary dermis	– Severe pain – Intact nerve endings in wound – Pain exacerbated by contact with surfaces	1–3 weeks, long term pigmentation changes may occur
Deep partial	Deeper reticular dermis	– Minimal pain – Nerve endings damaged but not completely destroyed – Endings have ability to transmit noxious stimuli	3–6 weeks with scars
Deep	Full thickness of skin and into the subcutaneous fat or deeper	– Minimal/pain free state – Complete destruction of nerves	Does not heal by primary intention and requires skin grafting

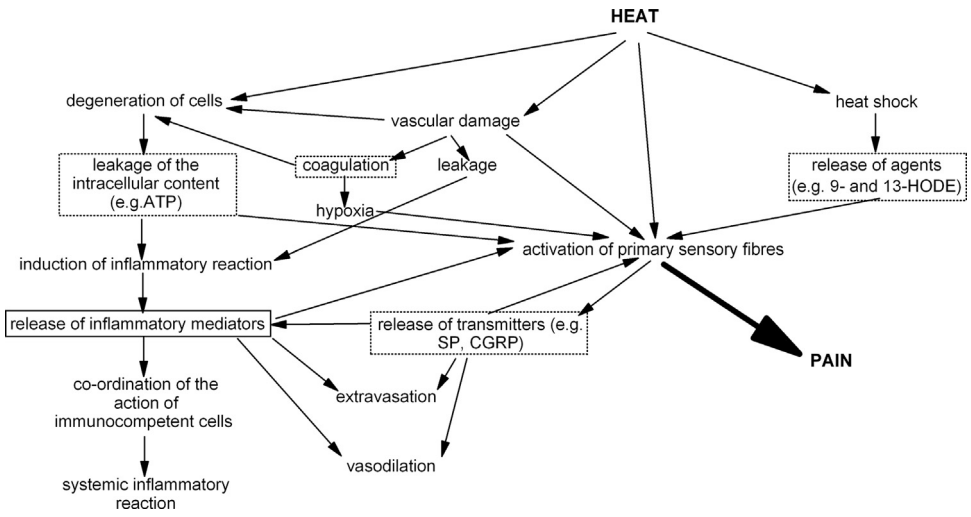

Fig. 1. Schematic drawing of event leading to the initiation, development and maintenance of pain following burn injury. The dashed line and solid line boxes identify events leading to the formation of the early and late burn injury tissue fluid.