Scandinavian Journal of Pain 4 (2013) 38–39

Contents lists available at SciVerse ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment

Sunburn—A human inflammatory pain model for primary and secondary hyperalgesia

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In this issue of the *Scandinavian Journal of Pain*, Rössler et al. describe an experimental model that confirms the central origin of pin prick hyperalgesia in the human sunburn model [1]. UV-irradiation has been used extensively as a translational model for inflammatory pain and hyperalgesia using rodents [2,3], pigs [4] and human volunteers [5,6]. The time course of hyperalgesia development is similar in different species, with an onset latency of 3–6 h and a peak responsiveness 24–48 h after irradiation, thus representing a useful experimental model for drug testing. Upon irradiation of small skin patches (about 1 cm^2), only primary hyperalgesia has been detected in human and rodents [2,3]. As a multitude of mediators are being released upon UV-irradiation of the skin, including eicosanoids (e.g. PGE2, PGD2, PGF2a, LTB-4, 12-HETE), cytokines (e.g. IL-1, IL-6, IL-8, TNF-alpha), growth factors (e.g. TGF-beta, VEGF, NGF) vasoactive amines and neuropeptides (e.g. histamine, bradykinin, CGRP), researchers have mainly focused on the primary hyperalgesia that is evident in the inflamed skin. Some of these can be accounted for the inflammatory UV-induced responses, such as erythema (i.e. CGRP) or heat hyperalgesia (e.g. PGE2, bradykinin) and sensitization of heat-sensing ion channels (e.g. TRPV1). Another cardinal symptom of UV-inflammation in human skin is a profound peripheral mechanical sensitization. There is recent evidence for a role of mechanical sensitization of heat insensitive (CM) fibers after UV-irradiation to particularly strong mechanical stimuli [3]. Primary mechanical hyperalgesia has been linked to CXCL5 in an elegant translational study [7].

In this issue, Rössler et al. describe a human UVB model in which they use larger irradiation areas [1]. Albeit no spontaneous pain is induced in the area of the sunburn, they found a large area of secondary mechanical hyperalgesia to pin prick in the subjects [8]. In order to prove the central origin, they used an anesthetic strip technique to exclude neuronal peripheral spread of hyperalgesia. The anesthetic strip did not reduce the area of secondary hyperalgesia, and thus, it can be assumed that it is of central origin. Experimentally, secondary mechanical hyperalgesia can be induced by activation of nociceptors by capsaicin or high current density electrical stimulation [9]. It is interesting to note that in the large sunburn model secondary hyperalgesia is induced without overt pain. It is assumed that a low level of activity in peripheral nociceptors is sufficient to sensitize spinal nociceptive pain processing but is not felt as overt pain as shown before for application of non-painful heat stimuli [10]. The particular value of the sunburn model in this respect is the endogenous origin of the peripheral mediators causing the nociceptor discharge. This is in contrast to experimental models that force nociceptor discharge by exogenous mediators such as capsaicin [11]. Thus, the model is expected to be responsive not only to anti-hyperalgesic compounds acting on spinal cord level, but also to anti-inflammatory agents that reduce the level of peripheral mediators and thus, the level of nociceptor discharge that induces and maintains central sensitization.

In summary, the human sunburn model can be used as an inflammatory model of primary hyperalgesia when small patches of skin are irradiated. Using larger areas the low level of nociceptor discharge is sufficient to cause central sensitization, but not high enough to cause overt pain. The particular value of the model is given by the fact that the local inflammatory mediators underlying sensitization and spontaneous activity are generated endogenously which facilitates the translation from the model to patients.

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DOI of refers to article: http://dx.doi.org/10.1016/j.sjpain.2012.09.001.
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1877-8860/$ – see front matter
http://dx.doi.org/10.1016/j.sjpain.2012.11.006

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