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EDITORIAL

Many parallels between itch and pain research

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Acute itch is a commonplace sensation elicited by insect bites and certain plants, and normally serves as a protective warning signal. However, chronic itch is a frequent symptom of dermatologic conditions and a variety of systemic diseases (for recent review, see LaMotte et al., 2014). Current treatments for chronic itch are poor, leading to suffering and diminished quality of life. The situation is not so different from that of chronic pain, although much less attention has been devoted to chronic itch which is all too often regarded as a purely dermatological problem that can be treated adequately by application of external remedies. This series of mini-reviews on different aspects of this topic in a journal devoted to pain research shall also foster a better understanding of chronic itch problems within the community of pain researchers and therapists.

The incidence of chronic itch and its socioeconomic costs have been the focus of recent epidemiological studies. In the United States, skin disease was estimated to affect upwards of one-third of the US population at any given time, imposing an economic burden of $96 Billion in 2004. A 2009 report from the US National Institutes of Health estimated chronic itch from atopic dermatitis alone to exact costs of approximately $3 Billion annually. A recent study reported a 22% lifetime prevalence of chronic itch among German citizens (Matterne et al., 2011). The negative impact of chronic itch is highlighted by Norwegian studies reporting an 8.8% incidence of chronic itch in adolescents, of whom 21.1% reported suicidal ideation (Halvorsen et al., 2012). This incidence of suicidal ideation is very similar to that of patients suffering from chronic pain, and markedly greater than that of subjects not suffering from chronic itch or pain (8.4%). Clearly, chronic itch is a major social and economic burden that demands research to establish more effective treatment strategies.

In 2005, the International Forum for the Study of Itch (IFSI) was established as an organization bringing together clinicians and researchers with interest in all aspects of itch, and a common goal to better understand the basic mechanisms of itch for the development of improved, evidence-based treatments. IFSI has grown to a current membership of over 150 individuals, and has biennial meetings as well as a growing presence at many dermatology and other scientific meetings worldwide. IFSI sponsored a symposium at the 23rd World Congress of Dermatology held in Vancouver in June 2015. This issue of the European Journal of Pain presents a series of mini-reviews submitted by world leaders in clinical and basic science who gave presentations at the IFSI symposium. This series of mini-reviews is an excellent representation of the broad spectrum of current issues related to understanding the epidemiology, psychology, pathophysiology and clinical treatment of itch.

There is a high prevalence of chronic itch associated with a variety of systemic diseases, including end-stage renal disease (ESRD) in patients undergoing kidney dialysis. Weisshaar reviewed recent studies that provide accurate estimates of the prevalence of chronic itch in ESRD (also known as uraemic itch). A recent cross-sectional study of over 800 ESRD patients reported a point prevalence of 25.2%, 12-month prevalence of 27.2% and lifetime prevalence of 35.2% of chronic itch in ESRD patients. This review provides valuable new information demonstrating the magnitude of debilitating chronic itch in ESRD that can be expected to only increase as the population ages. Chronic itch of ESRD and other causes are notoriously difficult to treat. Pongchareon and Fleischer provided an evidence-based analysis of efficacy of treatments for chronic itch of various aetiologies including uraemic itch. Using meta-analyses of randomized double-blind placebo-controlled studies in which itch intensity was measured and longitudinally tracked, they reported that nalfurafine and gabapentin were effective for reducing uraemic itch, naltrexone reduced chronic itch from cholestasis and atopic dermatitis, and ursodeoxycholic acid reduced itch from intrahepatic cholestasis of pregnancy. Other potentially useful drugs require larger or better

controlled studies, and some drugs including the 5-HT3 antagonist ondansetron were ruled out as having any antipruritic benefit. Continuing with the theme of chronic itch in systemic disease, Yosipovitch and Rowe reviewed chronic itch in malignancies associated with Hodgkin's lymphoma, polycythemia vera, non-melanoma skin cancer and cutaneous T-cell lymphomas, and currently available treatments. The prevalence of pruritus in squamous and basal cell carcinomas (43% and 33%) results in over one million new cases of malignancy-associated pruritus due to non-melanoma skin cancer per year, making this the most prevalent type of malignancy-associated itch.

Two more reviews are devoted to skin disease associated with chronic itch. Zeidler et al. review chronic itch associated with prurigo nodularis and its pathogenesis. Prurigo nodularis is a disease of the skin that is characterized by itchy nodules on the arms or legs and is a consequence of prolonged repeated scratching. In addition to changes in skin cells including hyperkeratosis, there is an increased density of nerve fibre innervating the affected skin that possibly contributes to the chronic itch, although the exact aetiology is not known. Szeptiekowski and Reich reviewed chronic itch associated with psoriasis. Psoriasis affects 1–2% of the world population and is typically manifested by demarcated papules and plaques distributed bilaterally. Psoriasis is very frequently accompanied by itch. Interestingly, itch in psoriasis has been linked with emotional stress, suggesting neuroimmune interactions. The aetiology is incompletely understood, but is postulated to involve neurogenic inflammation with increased levels of pruritic neuropeptides in the lesional skin, hyperkeratinosis, dysregulation of dermal opioids and increased nerve density. The latter may involve increased dermal expression of the nerve growth factor receptor Trk-A and decreased semophorin A (which inhibits neurite outgrowth). There are no effective treatments specifically dedicated to psoriatic itch, although blocking Trk-A appears promising.

A fascinating but poorly understood aspect of itch is that it can be strongly influenced by social setting, mood, stress, expectation, personality traits and other psychological factors. An example is 'contagious itch' in which one may experience itch and start scratching when observing someone else scratching. Schut et al. took advantage of this non-invasive means of eliciting itch and scratching in human subjects using audio-visual itch-evoking stimuli. They associated certain personality traits, such as 'agreeableness' and self-consciousness with enhanced itch and scratching in chronic itch patients. Focusing on oneself and concern about what others think were postulated to influence chronic itch patients to experience greater psychologically-induced itch and scratching. In contrast, healthy subjects did not show such associations, except for increased psychological itch in subjects displaying neuroticism. The authors also discussed the role of expectation in psychologically-evoked itch. It is well known that subjects receiving the same intensity of an experimental pain stimulus will give lower ratings if they anticipate that the stimulus will be weak (placebo effect), but will give higher pain ratings if they anticipate a strong stimulus (nocebo effect). The authors presented results of a new study using audio-visual stimuli to elicit itch and scratching. Intriguingly, atopic dermatitis patients who were informed that they would view videos that probably induce a very intense, extremely unpleaseant itch (catastrophizing group) displayed greater scratching compared to groups that were either informed or uninformed about the video. No such effect was observed in healthy subjects. These early studies suggest that expectations, personality and other psychological factors can influence itch, particularly in patients already suffering from ongoing itch. The mini-review by Bartels et al. further discussed placebo and nocebo effects in physically-evoked itch, which appear to be similar to short-term placebo and nocebo effects on pain perception. Verbal suggestions coupled with conditioning, i.e. pairing a neutral stimulus with an unconditioned stimulus that can be surreptitiously raised or lowered, produced long-lasting placebo and nocebo effects on itch perception, and even affected physiological responses such as wheal size. Personality traits related to negative outcome expectancies also appear to be important predictors of the magnitude of nocebo effects. Unlike pain, there are few studies so far of brain responses to itch-evoking stimuli under placebo and nocebo conditions; such studies are sorely needed.

Finally, Murota reviewed the effect of temperature on itch and possible physiological mechanisms. The capsaicin- and noxious heat-sensitive transient receptor potential channel TRPV1 is required for histamine-evoked itch. Murota made an interesting argument that endogenous mediators in inflamed skin are known to sensitize TRPV1, lowering its thermal threshold into the innocuous range. This provided a potential mechanism for innocuous warming to elicit itch in inflamed skin. However,

this effect may be limited to histamine-mediated itch, since most non-histaminergic itch mediators require a different channel, TRPA1, to elicit itch, and TRPA1 is not sensitive to heat. Involvement of calcitonin gene-related peptide (CGRP) in itch is also discussed. Noxious heat usually reduces itch in healthy skin but enhances itch in atopic skin. It is suggested that heat-evoked itch is a form of alloknesis. The term alloknesis was originally used to describe itch sensation elicited by a non-noxious mechanical stimulus such as gently stroking the skin. Artemin, which is expressed in atopic but not normal skin, contributes to epidermal neurite outgrowth, thermal hyperalgesia and speculatively also chronic itch. That artemin-treated mice exhibited excessive grooming behaviour when subjected to a warm (38 °C) environment is consistent with this possibility.

It is our hope that these interesting, informative and sometimes provocative mini-reviews will help to raise the awareness of itch among the readership of the European Journal of Pain, if not to stimulate a greater interest in research directed towards a better understanding of the mechanisms and therapeutic approaches to chronic itch as a deserving counterpart to chronic pain.

In conclusion, I express my gratitude to the authors for their excellent cooperation on a tight publication schedule, to Dr. Bettina Haake-Weber for her outstanding editorial assistance, and to the Editor-in Chief, Prof. Hermann Handwerker, for his inspiration and guidance for this special issue of the European Journal of Pain as well as his insight and leadership in the field of itch and pain mechanisms over the years.

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