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Chao Ma
Yuguang Huang *Editors*

Translational Research in Pain and Itch

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Preface

The past decade has witnessed exciting advances in the basic research of pain and itch – both are our most basic yet still mysterious sensations. Clinically, the treatment of prolonged and intractable pain (chronic pain) and itch (pruritus) cost billions of dollars every year worldwide while the results are often unsatisfying or accompanied with serious side effects. Despite the slow progress in drug discovery, scientists all over the world have recently acquired more insights into the mechanisms underlying pain and itch in both physiological and pathological conditions. The gaps between basic research and clinical application are eagerly waiting to be filled by translational research.

This book provides a comprehensive review of recent advances in the translational research on pain and itch. The contributing authors are world-renowned scientists and have made important discoveries in the relevant field of research. Their findings not only shed light on the mechanisms but also pave the way for developing novel strategies for the effective and safe treatment of chronic pain and pruritus. Hopefully not long from now, medical practitioners can be more confident and patients can be more optimistic when facing these annoying (and often terrible) conditions.

We sincerely appreciate all the contributing authors, our editorial team from the Joint Laboratory of Anesthesiology and Pain in Peking Union Medical College, and the Springer publisher. This book would not be possible without their time and effort.

Beijing, China

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Chapter 1
Assessment of Itch and Pain in Animal Models and Human Subjects

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Abstract For the past century, scientists have developed a variety of methods to evaluate itch and pain in both animal models and human subjects to throw light on some of the most important pathways mediating these unpleasant sensations. Discoveries in the mechanisms underlying itch and pain in both physiological and pathological conditions relied greatly upon these studies and may eventually lead to the discovery of new therapeutics. However, it was a much more complicated job to access itch and pain in animal models than in human subjects due to the subjective nature of these sensations. The results could be contradictory or even misleading when applying different methodologies in animal models, especially under pathological conditions with a mixed sensation of itch and pain. This chapter introduces and evaluates some of the classical and newly designed methodologies to access the sensation of itch and pain in animal models as well as human subjects.

Keywords Itch • Pain • Animal model • Human subject

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1.1 Introduction

Itch and pain are both unpleasant sensations that may indicate actual or potential tissue damage. Despite the ability to clearly discriminate between itch and pain in human subjects, it has never been an easy job to access such information in animal models. Itch, often defined as a "desire to scratch," is actually a multifaceted sensation. Although the general discourse mainly deals with histaminergic and nonhistaminergic itch (Davidson and Giesler 2010; Johanek et al. 2007), more sub-classifications could be beneficial. Pain faces a similar situation. In 1979, the International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Iasp 1979). This definition also clearly indicates that pain is a multidimensional experience. This chapter provides an overview of the methods used to assess experimentally induced itch and pain and analytically outlines the recently introduced animal models and human study protocols for itch and pain that have been reported in the research literature (Andersen et al. 2015).

1.2 Assessment of Itch in Animal Models and Human Subjects

Itch, also known as pruritus, is an unpleasant sensation that may prompt the sufferer to scratch the affected area that is aimed at alleviating or eliminating the effects of the stimulus and the on-going irritation or discomfort (Frese et al. 2011; Patel and Yosipovitch 2010; Shim and Oh 2008).

1.2.1 Assessment of Itch in Animal Models

1.2.1.1 Assessment of Itch in the Nape of Mice

An intradermal injection of histamine and capsaicin each elicited hind limb scratching behavior when injected into the nape of the neck of the mouse, indicated that there may be only one type of behavior toward an injection into the nape of the neck (Shimada and LaMotte 2008).

1.2.1.2 Assessment of Itch in the Cheek of Mice

In 2008, LaMotte's study modified Kuraishi model (Kuraishi et al. 1995) by administering intradermal injection of histamine and capsaicin, known to evoke predominantly itch and pain, respectively, in humans; each elicited hind limb scratching

behavior when injected into the nape of the neck of the mouse. When the same chemicals were injected into the cheek of the mouse, there were two site-directed behaviors: histamine elicited scratching with the hind limb, capsaicin evoked wiping with the forelimb, no crossover any more as happened in the nape intradermal injection (Shimada and Lamotte 2008).

Other pruritic chemicals, such as chloroquine, and cowhage spicules evoked both scratching and rubbing of the face, indicating a mixture of itch and nociceptive sensations after the application of these stimuli (Akiyama et al. 2010; Kim et al. 2011). Thus, the "cheek model" allows the animal to report differential responses to the application of a stimulus similar to the multiple choices available to humans. This could be advantageous in evaluating whether candidate therapeutic drugs applied to mice will be selective for blocking itch or pain in humans.

The cheek model might also be useful in determining whether an agonist selective for a specific isoform of a receptor elicits one type of site-directed behavior rather than a mixture of behaviors that might be evoked by a less selective chemical that activates multiple isoforms. For example, scratching the site of a histamine injection (Dunford et al. 2007) or an allergic contact dermatitis (Rossbach et al. 2009) on the rostral back of the mouse was reduced but not eliminated by either an H1 or an H4 antagonist. If the experiment were repeated on the cheek, it might be possible to determine whether the reduction produced by each antagonist was more related to pain, to itch, or to both.

1.2.1.3 Assessment of Itch in the Legs of Mice

In 2011 LaMotte's study, when different doses of histamine or capsaicin were injected into the calf of the mouse, there were two site-directed behaviors: capsaicin produced mainly licking, whereas histamine elicited more of a mixture of responses with more biting than licking for most animals (Lamotte et al. 2011), in which biting was characterized by contact of the incisors with the skin in a fairly high-frequency and low-excursion motion of the head. In contrast, licking was characterized by repeated protrusions of the tongue toward the skin over a longer excursion and lower frequency that could be readily distinguished from biting.

1.2.1.4 Assessment of Itch in the Eyes of Mice

Compared to other models described above, the eye model is relatively new and less used for itching research. However, it shows great potential for its obvious advantage: easy for experimenter to establish and measure. In fact, the eye model is mainly used in allergic conjunctivitis studies. The allergic conjunctivitis eye model was first established in guinea pig and then developed in mice (Laidlaw et al. 2002). Acute or chronic allergic conjunctivitis is induced by the instillation of histamine and other contact sensitizers (Nakano et al. 2009). Like many other models, scratching behavior is still the indication of an itch sensation in eye model. It has been

reported that ICR mice show the most marked scratching behavior in response to histamine; therefore, ICR mice are considered the most suitable strain for studying mediators and/or mechanisms for itching (Inagaki et al. 2001). A bout of eye scratching was defined as when a mouse stretched its hind-paw on the treated side toward its eye, leaned its head toward the paw, rapidly scratched its eye several times for approximately 1 s, and then lowered its hind-paw (Andoh et al. 2012).

The allergic conjunctivitis model might also be used to find candidate therapeutic drugs because it shows different symptoms by inhibiting specific receptors by selective antagonists. For example, histamine H1 receptor antagonists inhibited not only eye scratching behavior but also allergic-like symptoms such as edema and hyperaemia, while the histamine H4 receptor antagonist inhibited only scratching behavior induced by histamine (Nakano et al. 2009).

1.2.1.5 Assessment of Itch in the Rats

Similar methods have been applied to assess itch sensing in rats, although with fewer studies up to date (Table 1.1). In the cheek model, rats present the same behavioral responses to pruritogens and algogens as mice, that is, hind limb scratching and fore limb wiping, respectively (Klein et al. 2011). However, rats have a different pruritogen and algogen pattern compared with mice (Akiyama and Carstens 2013). For example, intradermal injection of histamine evoked pain-related behavior instead of itch sensing in rats. When injected intradermally in the rostral back, 5-HT and formalin stimulated hind limb scratching. In addition, cowhage spicules failed to elicit significant itch or pain behavior when injected into the cheek of rats (Klein et al. 2011). Other investigators (Minami and Kamei 2004) attempted to evaluate itch behavior in rat model in the eye, by applying eye drops containing histamine locally and creating a conjunctivitis model. However,

Table 1.1 Assessment methods and chemicals applied to evaluate itch in rats

Assessment methods	Application site	Behavioral response	Sense implication	Chemicals
Intradermal injection	Cheek	Hind limb scratching	Itch	5-HT, formalin, chloroquine, SLIGRL-NH2, capsaicin
		Fore limb wiping	Pain	Histamine, SLIGRL-NH2[a], capsaicin[a], AITC
	Rostral back	Hind limb scratching	Itch	5-HT, formalin
Cowhage spicules insertion	Cheek	Not significant	–	–
Eye drops dripping	Eye	Fore limb movements	Itch	Histamine

[a]SLIGRL-NH2 and capsaicin causes both itch- and pain-related behaviors in rats, therefore occurring in both boxes