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Itch Mediation and How It Differs from Pain

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Abstract
Itch, to most, is a common nuisance, although when chronic it can negatively affect quality of life. It is obvious that itch is processed differently than pain, but how it differs is not clear. Researchers have been trying to find a path that specifically mediates itch. They have found that itch is mediated through at least two different pathways: histamine dependent and histamine independent. However, many of the mediators involved in the transduction of itch also mediate pain. Although some itch-specific neurons have been found, the majority of the pruritogenic neurons are also responsive to pain stimuli. Two theories that can explain how the brain processes itch and pain as different sensations are the specificity theory and the selectivity theory.

Introduction

Itch is defined as "a stimulation of free nerve endings, usually at the junction of the dermis and epidermis of the skin, that evokes a desire to scratch." (Encyclopedia Britannica) Although most assume itch to be harmless, chronic itch can cause much discomfort and affect quality of life. Pain and itch are obviously different to the one experiencing either feeling, but whether these sensations are processed differently is not so obvious. Since the late nineteenth century when pain was discovered to be a real sensation, itch was thought of as just a weaker form of pain (Von Frey cited in Handwereker, 2014). Later, scientists found certain unmyelinated C-fibres of the dorsal root ganglion that were sensitive specifically to histamine (Schmelz, et. al. 1997). Similar histamine sensitive neurons were found in lamina I of the spinal cord (Andrew, Craig, 2001). This led to the specificity theory for itch, also called the labelled line theory, which proposes that different sets of neurons exclusively mediate itch or pain. However, many of the receptors that respond to itchy stimuli are also involved in mediating pain and later studies show that most of the neurons that respond to itch also react to pain producing substances (Shmelz, et.al.2003, Simons, 2004, Davidson, et. al., 2007, Akiyama, et. al.2009, Akiyama, et.al. 2010). So although itch and pain have separate pathways, a lot of overlap seems to exist between them.

Methods

This review was written through the critical analysis of clinical research papers and peer reviewed journal articles. The papers were found in searches on Google Scholar and access was obtained through the Touro College Library.

Discussion

Researchers first thought of itch as a milder form of pain, a theory known as the intensity theory. According to this theory, pain and itch sensations are mediated by the same neurons; if the stimulus is strong, there is a pain sensation, and if the stimulus is weak, an itch sensation (quoted in Patel, Dong, 2010). The basis for this theory was that cordotomy, surgical disconnection of the spinothalamic tract, leads to loss of both itch and pain on the contralateral side of the cut, whereas the perception of touch is impaired on the ipsilateral side (Nathan, 1990). This led to the theory that itch and pain are conducted along the same ascending pathway whereas mechanosensation travels along a separate path (quoted in Handwerker, 2014). However, many well-known characteristics of itch and pain don't seem to fit with this theory. For one, itch can be quite intense and never turn into pain, (Tuckett, 1982) and similarly, a painful stimulus does not feel like itch when administered at a lower intensity (Ochoa, Torebjork, 1989). More, the reflexes in response to pain and itch are quite different. The pain reflex is withdrawal, whereas the itch reflex is scratching. These observations seem to suggest that pain and itch have separate neural pathways.

One of the first steps in the advancement of itch research was the discovery of histamine. Histamine is released from mast cells and white blood cells, as a response to allergens or inflammatory mediators. A "triple response" to histamine was found. There is a local reaction, swelling, and also erythema, a flare, skin reddening around the affected skin (quoted in Handwerker, 2014). Histamine could be applied to specific regions and therefore allowed for the identification of the neurons which responded to it.

The breakthrough came in 1997, when using the new computer-assisted marking technique in microneurography, one group was able to identify histamine-sensitive C-fibers. Previous research had shown that itch had sometimes been induced during microstimulation in skin nerves where C-fibers were recorded. But most C-fibers identified were insensitive or only weakly responsive to histamine. The new technique was able to identify even small units that could not be identified with the old methods. Researchers identified 56 fibers in the superficial peroneal nerve of 52 healthy patients. Units were classified as mechanically and heat-responsive (CMH), heat-responsive (CH), or unresponsive to mechanical and heat stimulation (CMiHi). All of the fibers were tested by iontophoresis of histamine and the subjects rated the itch feeling. After the application of histamine, itch was usually felt 30-60 seconds after, reached a maximum after 2-3 minutes, and lasted for about 10 minutes. Twenty-three of the fifty-six units studied were not at all excited by the histamine. Twenty were weakly activated but their discharges did not match up with the time response of the subjects. Eight of the units (5 CH and 3 CMiHi) showed lasting responses to the histamine that coordinated with the time response of the

subjects. These neurons were found to have a much slower conduction velocity than the non- histamine responsive neurons, suggesting that these neurons are a class onto themselves. The units with histamine responses had a mean velocity of .52m/sec., compared to the .9m/sec. of the other units. The slow velocity reflects small axon diameters. Additionally, the units were found to have unusually large innervation territories. This finding explains the flare that is found after application of histamine (Schmelz, et. al. 1997).

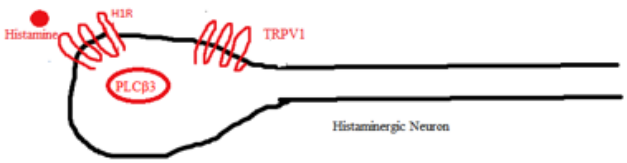
The next study that supported the idea of an itch-specific pathway was done on cats and found a population of histamine-selective lamina I spinothalamic tract (STT) neurons. The researchers obtained recordings from 190 lamina I STT neurons that had distal hind limb fields in the lumbosacral spinal cords of 33 cats. After categorizing these neurons into three main classes- nociceptive-specific, thermoreceptive- specific, and polymodal nociceptive- based on response to natural mechanical and thermal stimuli, there were 17 neurons left that were mechanically and thermally insensitive. Unlike the mechanically and thermally sensitive neurons, these neurons did not show spontaneous activity. These neurons were found to have a similar response time after histamine application to their innervation area of skin to the histamine selective neurons found in the previous study. The conduction velocities of these neurons were slower than the rest of the lamina I STT neurons, which is also consistent with the findings of the previously mentioned study. In addition, they all had large receptive fields, similar to the histamine selective fibers in the previous study. These characteristics that differed from the rest of the neurons seem to put these neurons into a class of their own. Some of the histamine-responsive neurons were tested with mustard oil, which causes a burning sensation, and some responded to it. Of those that responded to the mustard oil, most had responses that were much weaker than the response to histamine. The neuron that had a strong response to the mustard oil had been found to have a weaker response to histamine than the rest of the histamine-responsive neurons. Some of the histamine- responsive neurons did not respond at all to mustard oil, indicating that they are histamine-selective. (One should note, however, that the neurons were never tested with capsaicin, an algogen) (Andrew, Craig, 2001). This study and the one mentioned above both support the "specificity theory," as it seems like units were found that responded specifically to histamine.

Knowing that histamine is not the only pruritogen, a later study tested different pruritogens to see if the histamine-selective units would respond to them in accordance with pruritic potency of the pruritogen. They found that many histamine-selective units responded to the other pruritogens more than the non-histamine-selective units. However, they also found that the mechano- insensitive, histamine responsive units could also be excited by capsaicin and bradykinin, both algogens, albeit with a different response pattern than the CMH units. The mechano-responsive units had intense, short-lasting responses to capsaicin, whereas the mechano-insensitive units had longer lasting responses. This challenges the specificity theory as the itch units were activated by algogens (Shmelz,et.al.2003). Another study tested the responsiveness of STT neurons from the ventral posterior lateral nucleus of the thalamus in monkeys to different algogens and pruritogens. Neurons were found that responded to both histamine and capsaicin, another challenge to specificity, this time in the STT. (Simone, 2003)

As the pathway for itch becomes clearer and more defined, the question of how the brain processes the signals from the pathway as itch rather than pain remains uncertain.

The Histamine Dependent Pathway

Histamine binds with histamine receptors on free nerve endings. These receptors are classified into four subtypes, 1-4. In order to determine which of the four histamine receptors are responsible for the Ca2+ influx into the cell after the application of histamine, agonists of the different subtypes were applied with the histamine. The only agonist that stopped the calcium response was the histamine type-1 receptor (H1R) agonist, mepyramine (Nicolson, et.al. 2002). In pharmaceutical attempts to alleviate itch the H1R became the major target (Simons, 2004).



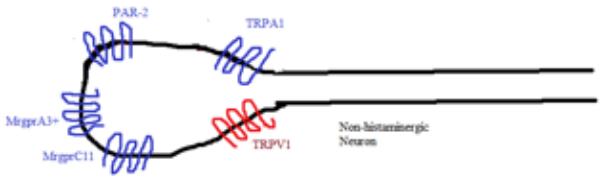
In the mediation of itch, H1R was found to activate phospholipase Cβ 3 (PLCβ3). PLCβ3 is expressed in neurons with histological markers for unmyelinated, C-fiber nociceptors. PLCβ3 is coexpressed with H1R in 90% of H1R neurons, suggesting that PLCβ3 may also be involved in the transduction of itch. Indeed, PLCβ3-deficient mice showed low Ca2+ release in response to histamine application, compared to the regular Ca2+ response to application of ATP, capsaicin, UTP, and bradykinin. In vivo testing showed that PLCβ3 deficient mice started scratching later and scratched less in response to histamine injection than wild-type mice. The PLCβ3 deficiency was most noticed when the H1R agonist, HTMT, was applied to the PLCβ3-deficient mice, and was compared to application of agonists of the other histamine receptors. The scratching response to HTMT was almost as low as the response to the control, saline injection. This indicates that PLCβ3 responds mainly to activity in the H1R receptor. Reduced scratching was also found in the response to

48/80, a substance that causes degranulation of mast cells and therefore the release of histamine (Han, et.al. 2006).

Activation of PLCβ3 causes increase in intracellular Ca2+ in the DRG neurons through the ion channel TRPV1. TRPV1, transient receptor potential vanilloid receptor-1, an ion channel, is a receptor that is found on free nerve endings and allows the action potential to occur by allowing Ca2+ into the neuron. Although TRPV1 was previously only known for its role in mediating pain, there were clues that it may also be involved in processing itch. For one, capsaicin, a major algogen that activates TRPV1, can cause itch when applied to the skin surface (Green, Shaffer, 1993). In addition, TRPV1 and histamine receptors are found on the same subset of neurons)Nicolson, et. al. 2002). Lastly, when high levels of capsaicin are applied to the skin, TPRV1 is desensitized and, interestingly, pruritus is also stopped (quoted in Shim, et. al. 2007). Indeed, studies show that TRPV1 has a role in mediating itch. When H1R or TRPV1 alone was transfected to HEK 293T cells, these cells did not respond to histamine. However, H1R and TRPV1 transfected together caused a large current in response to histamine application. Further, when capsazapine, a TRPV1 antagonist, was applied to the skin before histamine application, it caused smaller Ca2+ responses to histamine. In addition, TRPV1-deficient mice did not have a large increase in intracellular Ca2+ when histamine was applied, in contrast to wild-type mice who did. In vivo studies also proved TPRV1's involvement in the mediation of itch. Capsazapine given before histamine injection in mice resulted in reduced scratching to the histamine. Compared to wild-type mice, TRPV1-deficient mice also showed reduced scratching in response to histamine injection (Shim, et.al. 2007). These experiments demonstrate that TRPV1 plays a role in the transduction of itch.

The Histamine Independent Pathway

Although histamine plays a role in allergic itch, histamine is not the main pruritic mediator in most diseases of chronic itch (Klein, Clark, 1999). The use of H1R antagonists, antihistamines, are ineffective in stopping chronic itch (Twycross, et.al. 2003).



Chronic itch can be caused by the release of pruritogens from lymphocytes, mast cells, and eosinophils (Ikoma, et,al, 2006). In patients with atopic dermatitis, antihistamines did not suppress itch upon degranulation of mast cells. This suggests that there are mast cell itch mediators other than histamine (Rukweid, et.al. 2000). In addition, one of the regular characteristics of histamine induced itch, the flare, is missing in many types of itch (Ikoma, et. al. 2005). These findings point to another pathway for itch other than the mechano-insensitive C-fibres that mediate histamine induced itch.

Cowhage, the common name for the spicules that cover the tropical plant Mucuna pruriens, causes severe itch without a flare response (Johanek, et. al. 2007). It has been found in biochemical studies that mucunain, a proteinase in the cowhage, is what makes cowhage itchy (Reddy, et.al. 2008) In a study designed to test if histamine and cowhage activate the same C-fibres, all CMH units responded to cowhage, and none of the CMi, histamine responsive, units did, proving that cowhage and histamine do not activate the same fibres (Namer, et.al. 2008). Thus, cowhage has been used in many studies to understand histamine- independent itch.

Proteinases, such as mucunain, activate proteinase-activated receptors (PARs). A specific proteinase-activated receptor, PAR-2, has been identified on afferent nerve fibers (Steinhoff, et. al. 2000). PAR-2 is also activated by trypsin and tryptase. Tryptase is released by mast calls and trypsin is expressed in the skin (quoted in Shimada, et. al. 2006). The first study that found a connection between PAR-2 and itch was done on mice and found that PAR-2 played a major role in allergic dermatitis. PAR-2 deficiency led to reduced ear swelling. (Kawagoe, et.al. 2002) Patients with atopic dermatitis (AD) were found to have an increase in PAR-2 signaling, which was seen through higher levels of codeine-induced tryptase, PAR-2 expression on keratinocytes, and a greater response to PAR-2 agonist (Steinhoff, et.al. 2003). Another study found that itch was induced by PAR-2 agonist, a peptide, SLIGRL-NH2. When mice were injected with SLIGRL-NH2 they started vigorously scratching in levels much higher than when injected with saline vehicle. The application of an antihistamine, pyrilamine, did not reduce the scratching, confirming that PAR-2 is a receptor in non-histaminergic itch (Shimada, et.al. 2006).

One of the drugs used to treat malaria is chloroquine. Many patients complain about intense itch while taking chloroquine. The itch can be so intense that they stop taking the medicine. Antihistamines were ineffective in relieving the itch (quoted in Liu, et.al. 2009). Parts of the Mrgpr family (Mas related G-protein coupled receptors), a family of G protein-coupled receptors (GPCR), have been detected only on small-diameter sensory neurons in the DRG and TG. This would make them likely to be involved in the sensation of pain or itch. Itch induced by chloroquine was reduced in Mrpgr deficient mice, although the response to histamine induced itch was not significantly reduced in these mice. Further study found that the specific Mrgpr receptor for chloroquine was MrgprA3. BAM-822 was

found to excite MrgprC11 (Liu, et.al. 2009).

TRPA1, an ion channel, plays the same role in histamine- independent and chronic itch as TRPV1 plays in histamine dependent itch. That is, it allows the action potential to occur by allowing Ca2+ into the neurons. Researchers found that TRPA1 is greatly expressed in subset of TRPV1 positive neurons. Chloroquine and BAM-822 were found to activate the subset of TRPV1 neurons that also expressed TRPA1. Yet, neurons from TRPV1-deficient mice and neurons treated with capsazapine, a TRPV1 antagonist, both showed regular Ca2+ signaling in response to BAM and chloroquine. There was also no difference in action potential firing in response to chloroquine and BAM between TRPV1-deficient neurons and wild-type neurons. Thus, it is shown that the TRPV1 ion channel is not required for the mediation of BAM and chloroquine itch. However, TRPA1-deficient neurons had significantly decreased responses to both BAM and chloroquine. (As would be expected, they did have normal responses to histamine.) Further testing showed that the primary target for the MrgprA3 and MrgprC11 receptors was TRPA1. Interestingly, BAM and chloroquine have different mechanisms leading to activation of TRPA1. Thus, TRPA1 is downstream of different histamine- independent itch pathways (Wilson, et.al. 2011). Another study found TRPA1to be a vital mediator in chronic itch. Application of AEW (acetone/ether mixture with water) to the mouse cheek causes chronic itch-like symptoms in mice. It causes dry skin and increases scratching. It also causes epidermal thickening, a major symptom of chronic itch due to psoriasis in humans. Compared to wild-type mice, TRPA1-deficient mice showed significant reduction in scratching induced by AEW treatment. This is in contrast to TRPV1-deficient mice who after AEW treatment showed no decrease in scratching. Further, injection of TRPA1 inhibitor, HC-030031, into cheeck also caused reduction in scratching in AEW treated mice. These results show that TRPA1 is required in chronic itch. (Wilson, et.al. 2013).

One study used a novel approach to test if there are distinct histaminergic and non-histaminergic pathways. Instead of deleting certain receptors or neurons, this group used QX-314, a sodium channel blocker, to selectively "silence" specific receptors. When QX-314 was inserted into the mouse along with histamine, sodium currents in TRPV1 alone were blocked, thus temporarily "silencing" TRPV1. QX-314 inserted along with chloroquine had the same effect on TRPA1, silencing it. When TRPV1 was silenced, histamine induced scratching was stopped, but chloroquine induced scratching was regular, and when TRPA1 was silenced, chloroquine induced scratching was stopped. This confirmed the separate pathways for itch. (Roberson, et.al. 2013)

The above information has shown at least two DRG pathways for itch- histaminergic and non-histaminergic. A few other itch pathways were found, such as the pathway for β-alanine which is unique (Liu, et.al. 2012 b). Some other receptors have been found as well, such as toll-like receptor 7 (TLR7) and toll-like receptor 3 (TLR3). Although TLR7 knockout mice showed normal sensitivity to thermal and mechanical pain and showed normal scratching response to histamine-dependent pruritogens, scratching response to non-histaminergic pruritogens was significantly reduced (Liu, et.al. 2010). TLR3 knockout mice showed reduced scratching response to both histaminergic and non-histaminergic stimuli and TLR3 was found to be necessary in the development of chronic itch (Liu, et.al. 2012a). Another itch mediator found was the cytokine, interleukin-31 (IL-31). IL-31 is produced by T-cells and mice generated to overexpress it developed intense pruritus. IL-31 protein was fed to adult mice and within 3-4 days the mice developed severe pruritus (Dillon, et.al. 2004).

The separate histaminergic and non-histaminergic pathways continue into the spinal cord. In a study done on monkeys, 57 dorsal horn, STT neurons were tested for responsiveness to histamine and cowhage. Nineteen responded either to histamine or cowhage; none responded to both. This shows a continuation of the separate pathways. Interestingly, all pruritogen-responsive neurons also responded to capsaicin, further evidence against the specificity theory. As pointed out above, the study done on STT neurons that suggested the existence of histamine-specific neurons did not test for response to capsaicin, thus lacking evidence that those neurons did not respond to pain stimuli (Davidson, et. al., 2007).

Just like overlap was found in the neurons mediating pain and itch in the dorsal root ganglia, overlap was also found in the trigeminal ganglia (TG) and the trigeminal subnucleus caudalis of mice. Mice TG neurons were tested with different pruritogens, i.e. histamine, PAR-2 agonist, and 5-HT, and algogens, i.e. capsaicin and AITC. Using calcium imaging it was found that of 856 TG neurons, 15.4% responded to histamine and 5.8% to PAR-2 agonist. Although a small percentage of the pruritogenic neurons only responded to one pruritogen, the majority of those pruritogenic neurons responded to AITC or capsaicin as well, another finding that is inconsistent with the specificity theory. Consistent with the findings of different histaminergic and non-histaminergic pathways, most pruritogenic neurons were responsive to only one of the pruritogens. The majority of TG neurons that responded to pruritic stimuli were also responsive to algogens (Akiyama, et. al. 2010). Another study found neurons in the superficial dorsal horn that were responsive to PAR-2 agonist and 5-HT, yet most were also responsive to algogens (Akiyama, et.al. 2009).

As can be seen from the information presented above, many of the receptors in the itch pathways are also involved in the transduction of pain. TRPV1, PAR-2, TRPA1, and the TLRs all play roles in mediating pain. It has also been shown that algogens can activate pruritogenic neurons. It seems that there is no itch-specificity. However, two neurons have been found that seem to be itch-specific GRPR+ neurons and, more recently, MrgprA3+ neurons.

At the spinal level, gastrin-releasing peptide receptor, GRPR, has been found to be essential for mediating itch exclusively and not pain. GRP is expressed in a subgroup of dorsal root ganglion neurons. It is also colocalized with markers for unmyelinated fibers. In addition, approximately 80% of GRP+ neurons express TRPV1. GRP+ neurons are found only in the lamina I and II outer layer in the spinal cord. This data points to a possible involvement of the GRP signaling pathway in itch and pain. GRPR mutant mice were tested along with wild-type mice. GRPR mutant mice did not show a significantly different response from the wild-type mice to heat, pain, or mechanical stimuli. The mice were then tested with three different pruritogenic agents: 48/80, a PAR-2 agonist (SLIGRL-NH2), and chloroquine. After the separate injection of each pruritogen, a scratch count was taken from the mice. Although the GRPR mutant mice did scratch as a response to the injection, the number of scratches was significantly reduced, showing that GRPR mediates itch. To test whether activating GRPR at the spinal level would induce itch, GRPR agonist, GRP18-27, was intrathecally administered to the wild-type mice. It induced scratching behavior. As expected, the scratching response to GRP18-27 was significantly lower in GRPR mutant mice. In addition, when GRPR antagonist was inserted 10 minutes before the pruritogen in wild-type mice, scratching behavior was significantly reduced. Interestingly, the antagonist caused a lesser reduction in the effect of compound 48/80 than it had on PAR-2 agonist and chloroquine. This may be because PAR-2 and chloroquine act through a histamine-independent pathway, unlike compound 48/80. Since GRPR mutant mice showed regular pain responses to mechanical, thermal, and pain stimuli, but significantly reduced itch responses to pruritogens, GRPR+ neurons seem to be itch-specific (Sun, Chen, 2007). However, this does not rule out the possibility that GRPR neurons can also respond to pain and in GRPR mutant mice the loss of these neurons is compensated for by the other nociceptive neurons and therefore pain is still felt.

In order for something to be considered completely itch specific it needs to fulfill three criteria. First and most obvious, the neurons must respond to pruritic stimuli. Second, the loss of these neurons should only cause a loss of itch, not pain. Last, and most vital, only an itch response should be elicited when these neurons are specifically activated, not pain. The study done on the GRPR mutant mice fulfilled the first two criteria, but did not test for the third.

One group of neurons that was found to fit all the criteria is the MrgprA3+ neurons. These neurons only innervate the skin and were found to be absent from all other tissues, one clue that these neurons may be specific to itch, which is only felt on the epidermis. These neurons were coexpressed with TRPV1. They were also found to synapse with GRPR neurons in the spinal cord. These neurons responded to all types of itch other than β-alanine. When these MrgprA3+ neurons where ablated from a mouse line, the mice still showed regular responses to pain stimuli, though response to itch stimuli was greatly reduced. Mice have clearly distinct responses to itch and pain and therefore it is easy to know what sensation is being felt. Facial wiping with the forelimb is the response to pain, and scratching with the hindpaw is the response to itch (Shimada, LaMotte, 2008). (One interesting find was that the itch response to β-alanine was regular in MrgprA3+ -ablated mice, confirming that the neural pathway for β-alanine is unique.) In order to rule out the possibility that MrgprA3+ neurons are not necessary in pain response but can still be involved, MrgprA3+ neurons were specifically activated to see what response the neuron would elicit- pain or itch. The researchers used TRPV1-deficient mice and transfected TRPV1 only on the MrgprA3+ neurons. When capsaicin, an algogen, was injected into the cheek of these mice, the mice responded with scratching. This is in contrast to both wild-type mice that responded with wiping and TRPV1-deficient mice that did not respond at all. Thus it was shown that MrgprA3+ neurons coexpressed with TRPV1 elicit an itch response, regardless of the stimuli (Han, et. al. 2013). This is the first study to prove the existence of itch-specific neurons. No matter what the stimulus was, the sensation transmitted by those neurons was itch.

Conclusion

After the two initial studies that seemed to find itch-specific neurons, the support for the labelled line theory weakened. As seen above, many of the receptors for itch are also involved in the transduction of pain. Even more, itch responsive neurons in the DRG, TG, and the spinal cord also respond to algogens, such as capsaicin. However, with the finding of the MrgprA3+ itch-specific neurons, it is possible that the labelled line theory is correct for at least some of itch transduction. GRPR+ may also be part of this itch-specific group that mediates itch although further research would be necessary to confirm that. The study done on TG neurons also found a small population of pruriceptive neurons that only responded to pruritogens. Perhaps these pruriceptive-specific neurons are enough to mediate itch.

Even if itch is mediated through the few pruriceptive-specific neurons, it is still possible that the units that respond to both pruritogens and algogens also signal itch. Pruriceptive neurons are a subset of nociceptive neurons. Some hypotheses are that if the brain only receives input from the pruriceptive neurons, it processes the sensation as itch. However, if the brain is also receiving input from the nociceptive neurons, the brain only processes the pain and not the itch. So although those pruriceptive neurons are responsive to both pruritogens and algogens if there is no activity in the nociceptive-specific neurons when an itch stimulus is activating the pruriceptive neurons, itch will be felt (quoted in Patel, Dong, 2010). Along the same lines, another possibility is that the pain pathway activates mechanisms that inhibit itch transduction. Pain inhibiting itch is a familiar phenomenon, as it is well known that scratching relieves itch (Shmelz, et.al. 2003). A similar inhibition mechanism was suggested in the findings of a recent study. TRPV1 and TRPA1 both respond to algogenic stimuli. However, the study found that silencing one of them can cause algogens to elicit an itch response, i.e. scratching. This suggests that there can be inhibitors from the other ion channel that do not allow the brain to process the feeling as an itch (Roberson, 2013).

A final point for consideration is that most of these studies were done on animal models. But pain and itch may be mediated differently in different animals. Therefore, although research done on mice and other animals can give us an idea about the pathways in humans, further studies must be done to see how these mechanisms work in humans.

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