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Chronic pruritus: still a challenge but new directions of development have been indicated

Przewlekły świąd: nadal wyzwanie, ale nowe kierunki rozwoju zostały wyznaczone

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S u m m a r y

Pruritus is a subjective sensation which provokes a desire to scratch. This sensation can accompany a long list of dermatological, systemic, neurological or psychiatric disorders. Despite a high prevalence of pruritus, efficacious treatment of chronic itch remains a challenge due to its complex and multifactorial pathogenesis. However, recent decade has brought a rapid progress of itch understanding, giving us the hope for the development of new effective and well tolerated therapeutic strategies in the near future. In our review we have taken the opportunity to point out the most important findings from last years, that pushed forward our knowledge on pruritus and definitely will exert a significant impact on the diagnostic and treatment procedures of patients with chronic itch within the next few years.

Key words: itch, pathogenesis, treatment

S t r e s z c z e n i e

Świąd jest subiektywnym odczuciem, które wyzwala potrzebę drapania. Objaw ten może towarzyszyć długiej liście schorzeń dermatologicznych, ogólnoustrojowych, neurologicznych czy psychiatrycznych. Pomimo wysokiej częstości występowania świądu, skuteczne leczenie przewlekłego świądu nadal stanowi wyzwanie z uwagi na jego złożoną i wieloczynnikową patogenenezę. Odkrycia ostatniej dekady przyniosły jednak szybki postęp w rozumieniu świądu, dając tym samym nadzieję na rozwój w najbliższej przyszłości nowych, skutecznych i dobrze tolerowanych terapii przeciwświądowych. W niniejszym przeglądzie piśmiennictwa prezentujemy najważniejsze odkrycia ostatnich lat, które przyczyniły się do znacznego poszerzenia wiedzy o świądzie i niewątpliwie będą wywierać znaczący wpływ na postępowanie diagnostyczne i leczenie pacjentów z przewlekłym świądem w ciągu najbliższych kilku lat.

Słowa kluczowe: świąd, patogeneza, leczenie

INTRODUCTION

Pruritus is defined as a subjective sensation which provokes a desire to scratch. It could be acute (lasting less than 6 weeks) or chronic (with a 6 week duration or longer) (1). An acute pruritus may be considered as a defensive mechanism, that should protect our body from being hurt by insects or other parasites. On the other hand, a chronic itching represents a significant medical problem, responsible often for marked morbidity, quality of life impairment, and, in some patient population, even for increased mortality (2, 3). Pruritus seems to be a quite frequent symptom, as 8 to nearly 30% of participants of population based studies declared, that they have suffered from itching at least sometimes (4-7). This sensation can accompany not only a long list of skin diseases, but also a number of systemic, neurological or psychiatric conditions. Based on the newest itch classification proposed by the International Forum for the Study of Itch, pruritus could be divided into three major groups according to clinical manifestation: pruritus on primarily diseased, inflamed skin (group I), pruritus on primarily normal, non-inflamed skin (group II) and pruritus with chronic secondary scratch lesions (group III) (8). Furthermore, six categories of pruritus reflecting its pathogenesis have been defined, namely dermatologic, systemic, neurological, psychogenic, mixed and other type of pruritus (8). The new pruritus classification has unified previous attempts of itch categorization and, in addition, included clinical manifestation as an important

prerequisite of patient assignment. Therefore, it seems, that it is well fitted both for clinical, as well as for scientific purposes.

Despite a high prevalence of pruritus in general population, treatment of patients with chronic itch remains a challenge. It is related to a complex and multifactorial pathogenesis of this ailment. Antihistamines, the classic antipruritic drugs, are only effective in selected diseases, like urticaria or mastocytosis (i.e. in histaminergic itch), while in other pruritus forms they provide only partial relief or are not satisfactory at all (i.e. in non-histaminergic itch). However, recent decade has brought a number of crucial discoveries in itch knowledge which give a hope for the development of new effective therapeutic strategies in the near future.

PATHOPHYSIOLOGY OF PRURITUS

The exact pathomechanism of chronic pruritus is still not exactly known. For a long time, pruritus was considered as a subliminal pain, however, currently it is handled as a distinct sensation that admittedly shares some similarities and cross-linking with pain feeling, but possesses separate neurons dedicated solely for itch transmission (9-11). This hypothesis has been supported by a rapidly growing evidence arising over last years. In 2007 Sun et al. (12, 13) identified gastrin-releasing peptide (GRP)-positive dorsal root ganglion neurons, that were itch-specific. Expression of GPR receptors was restricted to lamina I of the dorsal spinal cord. Blockade of these receptors by direct spinal cerebrospinal fluid injection of a GRP receptor antagonist significantly inhibited scratching behavior in three independent itch models, while pain sensation evoked by various stimuli remained unchanged (12, 13). Similar effect was noticed by selective ablation of GRP-positive neurons (13). It was also shown, that these neurons are important to both histamine dependent and histamine independent pathways of itch, however, it seems that they mediated more non-histaminergic itch stimuli (14). Recently, attempts have been made to develop antagonists of these receptors that might be used as a potent antiprutic therapy in the future (15). Interestingly, transmission of itch stimuli by GRP-positive neurons was regulated by Toll-like receptors 3 (TLR-3), which represent other potential target for new antiprutic molecules to be developed (16). In addition, TLR-7, which is activated by imiquimod, has also been shown to mediate pruritus transmission in primary sensory neurons (17, 18).

Central transmission of itch is also modulated by endogenous opioid system. Central activation of μ-opioid receptors (MOR) (e.g. by opiates like morphine) produces pruritus, while activation of κ-opioid receptors (KOR) alleviates itch (19). A relief of itch or decrease of pruritus intensity may be expected during the blockade of MOR by naloxone or naltrexone (MOR antagonists) or by the stimulation of KOR by its agonists like nalfurafine or butorphanol (20-23). Unfortunately, central acting drugs may also produce a number of side effects, like nausea and vominiting, sleeping difficulty, fatigue and reversal of analgesia, which limits their wider use as antipruritic medications (19, 22). However, recent data showed that opioid receptors are also present on peripheral sensory neurons and partake in itch perception (24). As in central nervous system, activation of peripheral MOR produced itching, that could be effectively diminished by subsequent selective activation of peripheral KOR (24). A decrease of pruritus was also noticed after treatment with naloxone (a MOR antagonist) as well as naloxone methiodide (a peripherally restricted MOR antagonist) (24). Furthermore, Nelson et al. (25) reported that endogenous opioid-mediated antinociception in cholestatic mice is peripherally and not centrally mediated, again underlying the importance of peripheral opioid system in itch perception. In addition, Tominaga et al. (26) demonstrated that PUVA therapy diminished MOR immunoreactivity in the skin of patients with atopic dermatitis, and the degree of this decrease significantly correlated with pruritus improvement. It was also suggested, that pruritus in patients with psoriasis may be related to the imbalance of peripheral opioid system, as psoriatic patients with pruritus showed decreased expression of KOR and dynorphin A (the endogenous KOR agonist) within the epidermis in comparison to healthy controls, while the expression of MOR and β-endorphin (the endogenous MOR agonist) was similar in both groups (27). Thus, it seems, that higher MOR tone in the skin may be responsible for pruritus at least in some dermatological diseases. On the other hand, potentiating peripheral KOR activity via KOR selective ligands or inhibiting peripheral MOR would offer a new possibility of itch controlling (28).

A variety of other mediators released by skin cells (e.g. mast cells) were shown to be able to induce or modulate itch by activating approximately 5-20% of primary afferent itch-sensitive C-fibers, which can be divided into multiple subgroups based on pruritogen-sensitivity. A study on chloroquine-induced itch enabled to identify new pruritus receptors on C-fibers, namely Mrgprs, a family of G protein-coupled receptors that are expressed exclusively in peripheral sensory neurons (Mrgprs stays for Mas-related G protein-coupled receptors) (29, 30). These receptors may be activated by endogenous peptides, e.g. BAM8-22 (bovine adrenal medulla 8-22 peptide) and by exogenous substances (e.g. chloroquine) (29). Mice lacking a cluster of Mrgpr genes displayed significant deficits in itch induced by chloroquine but not by histamine. It seems, that Mrgprs are even more important for non-histaminergic itch, than PAR (protease activated receptors), that were also linked with chronic itch sensation (31, 32).

Another promising molecule, that has also recently been identified as an important pruritogen, especially in inflamed skin, is interleukin 31 (IL-31) (33, 34). There was a good correlation between the scratching counts and expression of IL-31 mRNA in mouse model of atopic dermatitis (35) and anti-IL-31 antibodies effectively reduced scratching behavior in these animals (36).

It was also clearly demonstrated, that IL-31 is an important cytokine in atopic dermatitis in human, and its level correlated with disease severity, sleeplessness, serum IgE level, and subjective itch intensity (37-39). Allergen-induced pruritus may also be inhibited, at least partially, by histamine blockade. However, it seems, that histamine is able to produce itch both via H1 receptor, as well as due to activation of newly described and cloned H4 receptor (40-43). Importantly, blockade of both receptors provided greater pruritus relief than single receptor inhibition (41, 43). Interestingly, the inhibitory effect of H4 receptor antagonist was greater than those observed with H1 receptor antagonists and histamine H4 receptor-mediated pruritus was shown to be independent of mast cells or other hematopoietic cells and may result from actions on peripheral neurons (40). Thus, it could be supposed, that H4 receptor antagonists may be tried in chronic pruritic diseases where H1 blockers were not enough effective (40).

Describing the pathomechanism of itch it can not be forgotten, that to be noticed, each stimulus, including a pruritic one, must be processed by a human brain. It was shown, that acute histamine-induced itch co-activates the anterior cingulate cortex, the insular and primary somatosensory cortices, premotor and supplementary motor areas, cerebellum and thalamus (44-46). However, what is even more important, recent findings demonstrated, that patients suffering from chronic itch showed different brain activation upon acute itch compared to healthy controls. Patients with atopic dermatitis showed higher activity in the contralateral thalamus and in the ipsilateral basal ganglia, while healthy controls had higher activation in the ipsilateral premotor cortex (45, 46). Moreover, the activity in cortical areas involved in affect and emotion correlated to measures of disease severity (46). It seems, that different brain activation might be responsible for itch chronicity and this problem has to gain more attention in the future in order to be able to effectively treat chronic itch.

MEASUREMENT OF PRURITUS

Measurement of pruritus is a big challenge due to subjective character of this sensation. A sophisticated methods, like nocturnal wrist measurements or infrared camera videotaping, have been used to provide more objective assessment of itch intensity, however, this methodology is expensive, time consuming, and results are difficult to interpret (47). In addition, it only enables evaluation of nocturnal pruritus and is not fitted to itch, that is present during a day. Therefore, nocturnal wrist measurement is not widely used even in scientific studies. Assessment of brain activity during itch episodes is another possible option to document objectively pruritus, however, the current data are rather preliminary, and there is a great variability of achieved results with different diagnostic techniques, which are also too expensive to be used as a routine diagnostic procedure (44-46).

To make the assessment of pruritus intensity more reliable with subjective instruments, the International Forum for the Study of Itch has initiated two projects dedicated itch measurement. The first one is concentrated on the development of an international, widely-accepted itch questionnaire, which might be used in clinical trials. Recently, this group has published first consensus paper which defined major elements, that should be included in such questionnaire (48). Hopefully, in the near future they will be able to present their new questionnaire, that will be free of limitations that current questionnaires have.

The second study was initiated to validate the visual analogue scale (VAS) and numeric rating scale (NRS) as measurements of itch intensity. The VAS is a 10 cm long line, on which patients indicate the intensity of pruritus by crossing the line at the point that corresponds to their pruritus severity, being informed that the beginning of the scale refers to no pruritus (0 points) and the end of the line to the most intense pruritus (10 points). With NRS patients assess verbally their pruritus from 0 (no pruritus) to 10 (the most intense itching they can imagine). Both instruments have been used for a long time to assess pruritus severity, but had never been tested before, whether they provide valid results on itch. Based on two independent studies which have been recently published, it could be now confirmed, that both scales are reliable methods of pruritus assessment, however, they are not simply interchangeable (49, 50). According to the study of Reich et al. (50) following categories could be defined: 0 – no pruritus, > 0 but < 4 points – mild pruritus, ≥ 4 but < 7 points – moderate pruritus, ≥ 7 but < 9 points – severe pruritus and ≥ 9 points – very severe pruritus. Usually the patient should be asked regarding the pruritus intensity within the last 3 days. It seems, that patients had less problems with NRS than with VAS, therefore, prior to the itch evaluation with VAS, the patient should be thoroughly instructed, how to assess pruritus on this scale. If the diary is needed, twice daily assessment of pruritus seems to be the most reliable method (51). According to current data it could be postulated, that monodimensional instruments like VAS and NRS should be used in daily routine practice, as they provide rapid and valid data on itch intensity. However, in clinical trials they have to be supplemented with other instruments assessing itch quality, depression or anxiety problems, quality of life or patient demands regarding the therapy (52).

UREMIC PRURITUS

Uremic pruritus is a common complaint of patients with chronic renal failure undergoing dialysis. It is present in about 40 to 70% of dialysis patients (53). Although a number of potential hypotheses have been formulated for years, the pathomechanism of uremic pruritus remains unknown. Currently it seems that the cause of this sensation is rather multifactorial, including skin dryness, abnormal skin innervation, bivalent

ion imbalance, disturbances of mast cell functioning including abnormalities of tryptase/chymase positive vs. tryptase positive/chymase negative mast cell homeostasis, concurrent systemic inflammatory process, and such potential itch mediators and hormones like parathormon, histamine or serotonine (53, 54).

Despite the exact mechanism of uremic pruritus remains to be elucidated, over the last decade several new treatment modalities have been demonstrated to effectively diminished its severity. Uremic pruritus in many patients may be reduced by regular moisturizing the skin with various emollients (55). Furthermore, a number of topical agents, like 1% pramoxine, 2.2% gamma-linolenic acid, and endocanabinoids were shown to be effective, well tolerated and safe in the treatment of uremic pruritus (56-58). However, what is even more interesting, some new systemic therapies were demonstrated to be efficacious as well. The therapy which is worth to try in subjects with uremic pruritus is gababentin or pregabalin. In one randomized controlled study on 25 adult patients gabapentin reduced itch intensity from 8.4 ± 0.9 points to 1.2 ± 1.8 points according to VAS ($p < 0.001$) (59). Next studies confirmed this encouraging finding (60-62). Pregabalin, another drug acting on GABA-ergic neuronal transmission, has also been shown to significantly reduce pruritus in patients on maintenance dialysis (63).

As mentioned above, chronic pruritus may be related to the imbalance of endogenous opioid system, as activation of MOR induces pruritus, while activation of KOR exerts a contrary effect. These observation led to the development of KOR agonists, which exemplify another new treatment strategy for patient with refractory uremic pruritus (64). Two independent double-blind placebo-controlled, randomized studies shown the usefulness of nalfurafine, a selective KOR agonist, in reducing the intensity of uremic itch. In the study by Wikström et al. (65) on 144 dialysis patients statistically significant reductions of worst itching ($p = 0.02$), itching intensity ($p = 0.04$), sleep disturbances ($p < 0.001$) as well as improvement of excoriations ($p < 0.01$) were noted in the group receiving intravenous nalfurafine (5 μg i.v. 3/week for 2 or 4 weeks) as compared with placebo. Importantly, nalfurafine showed similar types and incidence of drug-related adverse events as did placebo in these severely ill patients (65). In another trial by Kumagai et al. (66) enrolling 337 subjects with uremic itch significant reduction of pruritus severity was observed in both groups receiving oral nalfurafine in the respective dose of 2.5 μg and 5.0 μg compared to placebo. The incidence of adverse drug reactions was 35.1% in the 5 μg group, 25.0% in the 2.5 μg group and 16.2% in the placebo group, with the sleep disturbances being the most common adverse event due to nalfurafine treatment (66). Based on these observation, nalfurafine has recently been approved for treatment of uremic pruritus in Japan. Whether nalfurafine may also be used for another diseases needs to be elucidated in the future.

CHOLESTATIC PRURITUS

Cholestatic pruritus is another form of itching that is related to a systemic disorder, namely cholestasis and liver dysfunction. The prevalence of cholestatic pruritus may vary between different liver diseases, being the most common in primary sclerosing cholangitis and primary biliary cirrhosis. Until recently this symptom was linked with various substances, like bile salts, progesterone metabolites, histamine, endogenous opioidergic peptides and many others (53). However, in 2010 a group of researchers from Netherlands documented, that during cholestasis an increase of autotaxin activity may be found in patients sera, that correlated with pruritus intensity (67). Autotaxin is an enzyme that converts lysophosphatidylcholine into lysophasphatidic acid (LPA), a potent neuronal activator, which was also markedly increased in patients with intrahepatic cholestasis of pregnancy versus pregnant controls ($p < 0.001$) and cholestatic patients with versus without pruritus ($p < 0.001$).

In patients with primary biliary cirrhosis who underwent temporary nasobiliary drainage, both itch intensity and autotaxin activity markedly decreased during drainage and returned to preexistent levels after drain removal (67). Furthermore, concurrently to reduction of autotaxin activity due to administration of rifampicin, pruritus intensity also significantly diminished, a finding that further confirmed the important role of this enzyme and LPA in cholestatic itch (68). Interestingly, autotaxin activity was deregulated only in cholestatic pruritus, but not in other forms of systemic itch (68). Thus, autotaxin and LPA represent very interesting and promising therapeutic targets for the development of effective therapeutics for cholestatic pruritus in the future. However, until this happens, treatment options for cholestatic itch by now include the use of anion exchange resins like cholestyramine, colestipol and colesevelam, ursodeoxycholic acid, the microsomal enzyme inducer rifampicin, the opioid receptor antagonists – naltrexone and naloxone, and the serotonin reuptake inhibitor – sertraline (69, 70). Sometimes, to achieve satisfactory itching reduction a combinational therapy has to be applied.

SUMMARY

Pruritus is a symptom which may accompany a number of dermatological, systemic and neurological conditions. The effective therapy of itching depends on the underlying condition, patient general status and the available treatment options. In many diseases successful antipruritic therapy remains a challenge, however, over the past few years a rapid progress has been made in the understanding of the pathophysiology of this sensation. These new findings give a great hope for the development of more efficacious antipruritic treatment strategies in the near future.

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received/otrzymano: 22.08.2012
accepted/zaakceptowano: 28.09.2012

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