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REVIEWS

Pruritus in Cholestasis: Facts and Fiction

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Pruritus is a common symptom in patients with cholestatic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, intrahepatic cholestasis of pregnancy, or hereditary pediatric cholestatic disorders and may accompany, although less frequently, many other liver diseases. Recent findings indicate that lysophosphatidic acid (LPA), a potent neuronal activator, and autotaxin (ATX; ectonucleotide pyrophosphatase/phosphodiesterase 2), the enzyme which forms LPA, may form a key element of the long-sought pruritogenic signaling cascade in cholestatic patients suffering from itch. Serum ATX, but no other pruritogen candidate studied so far, correlates with pruritus intensity and responds to therapeutic interventions. In this comprehensive review, we provide a short update on actual insights in signal transmission related to pruritus and discuss pruritogen candidates in cholestasis. We also summarize evidence-based and guideline-approved as well as experimental therapeutic approaches for patients suffering from pruritus in cholestasis. (HEPATOLOGY 2014;60:399-407)

Pruritus (itch) is a frequent and sometimes agonizing symptom accompanying various liver diseases, particularly cholestatic disorders (Table 1).[1] Pruritus may be mild and tolerable, but may also dramatically reduce quality of life, cause severe sleep deprivation, depressive mood, and may even induce suicidal ideations in those patients most affected.

A diurnal variation of itch intensity is reported by a vast majority of patients, with most intense itch in the late evening and early at night. A diurnal variation was convincingly proven by piezoelectric analysis of scratch intensity in patients with primary biliary cirrhosis (PBC).[2] Typical localization of itch is reported at the limbs and soles of the feet and palms of the hands, but generalized pruritus may also occur. Primary skin lesions are not observed in cholestatic patients with pruritus. Still, intense scratching may induce secondary excoriations and prurigo nodularis.

The search for the potential pruritogen in cholestasis has been ongoing for more than 2000 years, when Aretaeus the Cappadocian (2nd century B.C.) stated that "pruritus in jaundiced patients is caused by prickly bilious particles."[3] Our state of knowledge at the start of the 21st century was not much different. Still, clinical observations during the last 30 years have led to the conclusions that potential pruritogens 1) accumulate in the systemic circulation as indicated by (partial) relief of severe pruritus after treatment with plasmapheresis, albumin dialysis (e.g., MARS), or plasma separation/anion absorption; 2) are secreted into bile as suggested by attenuation of pruritus after oral administration of the anion exchange resin cholestyramine or proven by rapid relief of most severe, treatment-refractory pruritus after nasobiliary drainage; 3) are (biotrans-)formed in liver and/or gut as indicated by effective treatment with the potent pregnane X receptor (PXR) agonist, rifampicin; and 4) affect the endogenous opioidergic and serotoninergic system as suggested by mild antipruritic activity of opioid antagonists such as naltrexone and serotonin reuptake inhibitors such as sertraline.[1-3]

Novel findings during the past 5 years have renewed our view on the pathogenesis of pruritus. Here we aim to critically review the actual knowledge on the molecular pathogenesis of pruritus in cholestasis. We will

Abbreviations: ATX, autotaxin; DRG, dorsal root ganglia; Enpp2, ectonucleotide pyrophosphatase/phosphodiesterase 2; GRP, gastrin releasing peptide; HPETE, 5-hydroperoxy-eicosatetraenoic acid; ICP, intrahepatic cholestasis of pregnancy; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; Mrgpr, Mas-related G protein coupled receptors; Nppb, natriuretic polypeptide b; PBC, primary biliary cirrhosis; PXR, pregnane X receptor; TRPV1, transient receptor potential cation channel subfamily V member 1 (also known as capsaicin receptor).

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also summarize actual evidence-based therapeutic recommendations.

New Insights in Signal Transmission of Pruritus

More than 350 years ago itch was first defined by a German physician, Samuel Hafenreffer, as an unpleasant sensation that makes people want to scratch. This definition still holds and renders pruritus a complex sensory modality. Indeed, research into the mechanism of itch made only recently some fundamental progress.

Itch-Specific Neural Pathways. Until the late 1990s it was assumed that itch perception is transmitted by way of pain fibers. Subliminal pain signals would be perceived as itch and itch was entitled "pain's little brother." However, this concept is no longer adhered to after several recent discoveries that are key to our understanding of itch.[4] Evidence for a separate itch-sensitive subgroup of mechano-insensitive C-nociceptors with unmyelinated nerve endings in the skin was provided using microneurography.[5] These C-fibers transmit the signals from the skin through the dorsal root ganglia to a second neuron in the dorsal horn of the spinal cord, crossing to the contralateral side and projecting by way of the spinothalamic tract to the ventromedial nucleus of the thalamus. Finally, the itch signals are transferred to the primary sensory cortex, supplementary motor area, anterior cingulate cortex and inferior parietal lobe (Fig. 1).[6]

Notwithstanding the fact that itch and pain are transmitted by way of different afferent fibers, these fibers appear to have a lot in common. Itch as well as nonmechanical pain transmission involve the activity of the capsaicin receptor, TRPV1. TRPV1 was discovered as a receptor sensing not only capsaicin, the active compound of red hot chili pepper, but also high temperature (>43°C), low pH (<5.9), and a number of endogenous signaling molecules such as endovanilloids, lipoxygenase products such as 5-hydroperoxy-eicosatetraenoic acid (HPETE), and many others. TRPV1 is regulated by PI3 kinase, protein kinase A and C. Hence, this nonspecific cation channel appears to be an integrator of pain and itch transmission.[7]

Lysophosphatidic acid (LPA), which was recently recognized as a potential mediator in cholestatic itch (see below), is capable of directly activating TRPV1.[8] In patch clamp studies, LPA stimulates TRPV1 channel opening but does so considerably faster and stronger in inside-out membrane patches (i.e., intracellular signaling) than in right side-out patches (i.e., extracellular signaling). LPA seems to interact with a proposed intracellular PIP2 binding site on TRPV1 in which the lysine 710 residue participates. Thus, these studies address a role for intracellular rather than extracellular LPA. Since LPA is a relatively hydrophilic lipid molecule, it remains to be shown how relevant this type of activation is with regard to extracellular generation of LPA.

Pain has an inhibitory effect on itch. This phenomenon is illustrated by the fact that antinociception (epidural morphine) frequently causes itch in the region of reduced pain transmission (although signaling through the μ-opioid receptor isoform MOR1D may also contribute[9]). The level at which this occurs is most likely the spinal cord, since mice with a deletion of the *Bhlhb5* gene display severe chronic itch. Bhlhb5 is a transcription factor that is transiently expressed in the dorsal horn of the spinal cord and deletion of its gene leads to the absence of inhibitory interneurons in the dorsal horn.[10] This observation demonstrates that a tonic activation of these interneurons (most likely by signals from pain neurons) suppresses itch transmission.

Itch-Specific Neurotransmitters and Receptors. The concept of itch-specific nerve fibers is supported by several molecular and genetic studies in mice which also highlight that nerve endings express a host of receptors which, when activated, give rise to itch perception.

Gastrin-releasing peptide (GRP) is one of the specific itch neurotransmitters and is expressed in lamina 1 of the dorsal spinal cord.[11,12] Mice in which GRP-receptor expression was disrupted had normal (thermal) pain but decreased itch perception from various pruritogens.[11,12]

Natriuretic polypeptide b (Nppb) also functions as an itch-specific neuropeptide.[13] *Nppb*$^{-/-}$ mice were healthy, had normal numbers of nociceptive, touch, and proprioceptive neurons, and the distribution and number of dorsal horn interneurons was unaffected.[13]

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Table 1. Examples of Hepatobiliary Diseases Typically Associated With Pruritus

Hepatocellular cholestasis:
intrahepatic cholestasis of pregnancy (ICP)
estrogen-, progesterone- or testosterone-induced cholestasis
toxin- or other drug-induced hepatocellular cholestasis
benign recurrent intrahepatic cholestasis (BRIC)
progressive familial intrahepatic cholestasis type 1 and 2 (PFIC1, PFIC2)
chronic viral hepatitis C
(noteworthy, parenteral nutrition-induced cholestasis, chronic hepatitis B, alcoholic or nonalcoholic fatty liver disease (NAFLD) are not or only exceptionally accompanied by itch)
Cholangiocellular cholestasis (with intrahepatic bile duct damage):
primary biliary cirrhosis (PBC)
primary sclerosing cholangitis (PSC)
secondary sclerosing cholangitis
sarcoidosis
ABCB4 deficiency (including PFIC3)
Alagille syndrome
drug-induced small duct cholangiopathies
(noteworthy, ductal plate malformations such as biliary hamartomas [von Meyenburg complexes], Caroli syndrome, and congenital liver fibrosis are typically not accompanied by itch)
Obstructive cholestasis:
gallstone disease
primary and secondary sclerosing cholangitis (PSC, SSC)
IgG4-associated cholangitis
biliary atresia
cholangiocellular carcinoma
benign bile duct adenoma
hilar lymphadenopathy
pancreatic head carcinoma

However, the response to injection of pruritic agents such as histamine, chloroquine, endothelin, and others was strongly impaired, indicating that Nppb functions as a general neurotransmitter for itch.[13] GRP was shown to act downstream of Nppb. Hence, a model was proposed in which primary pruriceptive neurons (in dorsal root ganglia) release Nppb to activate secondary pruriceptive neurons (in the dorsal horn) that express the natriuretic receptor a; these in turn release GRP to activate tertiary pruriceptic neurons (Fig. 1).[13]

The murine Mas-related G protein coupled receptor (Mrgpr) A3 is involved in activation of primary sensory neurons by pruritogens.[14] MrgprA3 is responsive to pruritogenic compounds such as chloroquine and exclusively expressed in sensory neurons in the epidermis of skin. About 90% of these MrgprA3$^+$ neurons also expressed TRPV1, whereas the total TRPV1$^+$ population was much larger.[14] Ablation of all MrgprA3$^+$ neurons led to substantial reductions in scratching behavior evoked by multiple pruritogens but left pain perception unaffected. Conversely, mice in which TRPV1 was exclusively expressed in MrgprA3$^+$ neurons exhibited itch but not pain behavior in response to capsaicin.[14] This confirms that TRPV1 relays itch signals in itch neurons and pain signals in C-fibers programmed for pain transmission. It was demonstrated that these MrgprA3$^+$ neurons form synapses with neurons that are positive for GRP, indicating that GRP is a downstream neurotransmitter of MrgprA3$^+$ neurons.[14]

Together, these studies have revealed several receptors and signaling molecules as being involved in acute forms of pruritus in mice and men, but information on the role of specific pruritogens in chronic human disorders is very sparse.

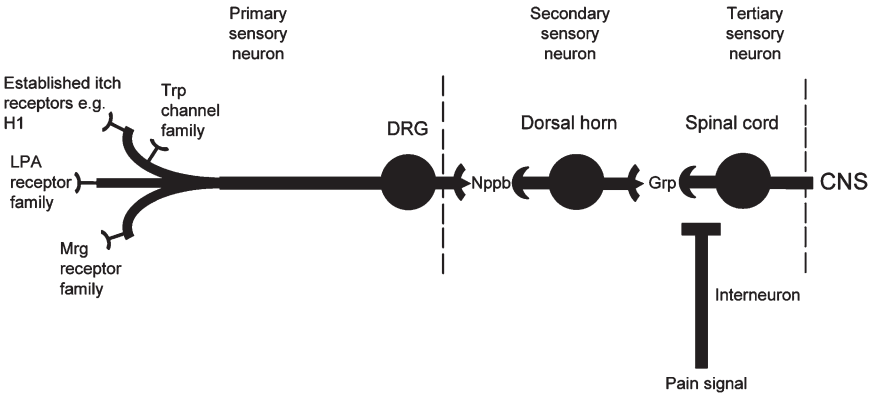

Fig. 1. The itch neuron. Schematic representation of receptors and neurotransmitters that may play a role in itch transmission. Pruritogens may bind to their receptors on unmyelinated itch nerve endings in the skin. This may involve established receptors such as the histamine receptors, PAR2, IL-31 receptor, and others but also newly discovered receptors, such as those from the transient receptor potential (TRP family, TRPV1, and TRPA1) or from the Mas gene related (Mrg) family, that are activated by endogenous and exogenous small molecule pruritogens. Itch may also be initiated or potentiated by activation of LPA receptors. Synaptic transmission between the primary and secondary itch neurons may be mediated by Nppb, while transmission between the secondary and tertiary neuron may involve Grp. Finally, at the level of the spinal cord itch transmission is dampened by pain signals. CNS, central nervous system; DRG, dorsal root ganglia; Grp, gastrin releasing peptide; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; Mrg, Mas-related G protein coupled; Nppb, natriuretic polypeptide b; Trp, transient receptor potential cation channel.

Pruritogen Candidates in Cholestasis

In the past, a variety of molecules such as bile salts, endogenous opioids, histamine, serotonin, and various steroid metabolites have been discussed as potential pruritogens in cholestasis (Table 2; see previous reviews).[2,3] Serum and/or tissue levels of these suspects have never been found to closely correlate with itch intensity, making it less likely that they really are *the* candidates responsible for itch in cholestasis. Some of them might rather modulate than initiate the complex signaling chains leading to the desire to scratch. We refer to previous reviews regarding the potential role (or not) of histamine, serotonin, or endogenous μ-opioids in cholestasis-associated pruritus.[2,3]

LPA and Autotaxin (ATX). More recently, we were able to unravel that LPA is a potential candidate for the initiation of itch in cholestasis.[15] We had hypothesized that if a pruritic factor exists in serum of patients with pruritus due to cholestasis, this factor should potentially activate neuronal cells. We therefore exposed various neuronal cell lines to sera of pruritic and nonpruritic cholestatic patients as well as healthy volunteers and compared the cytosolic free Ca^{++} ($[Ca^{++}]_i$) response as a simple marker of cell activation. We detected a particularly strong $[Ca^{++}]_i$ response induced by sera of women with intrahepatic cholestasis of pregnancy (ICP).[15] Chemical analysis revealed that the neuronal activator in these sera was not a peptide, had a molecular weight below 3 kDa, was amphiphilic with increasing hydrophobicity upon protonation, and acted by way of G-protein coupled receptors. Our best guess that the molecule was LPA was verified by repression of the serum-induced neuronal activation by a LPA receptor blocker, and demonstration of elevated levels of LPA in sera of women with ICP.[15] In addition, a causative role for LPA was suggested by the finding that intradermal injection of LPA but not vehicle initiated a scratch response in mice, only confirming a previous independent study in mice.[15,16] Of note, LPA was rather unstable in serum and increased in concentration upon storage, most probably due to formation from its precursor lysophosphatidylcholine (LPC). Therefore, we determined the activity of the lysophospholipase D, ATX, which is responsible for formation of LPA from LPC.[17,18] ATX is the main source of circulating LPA levels.[19] ATX belongs to the family of ectonucleotide pyrophosphatases/phosphodiesterases (ENPP1-7) and is also referred to as ENPP2. This large glycoprotein is synthesized as a pre-proenzyme and, in contrast to all other ENPPs, secreted to the extracellular space upon two N-terminal cleavages.[20] As a pyrophosphatase ATX hydrolyzes nucleotides, but with a much lower affinity compared to lysophospholipids.[21] The specificity for LPC as a substrate is probably further increased by the fact that formed LPA remains in the binding pocket, thereby inhibiting the enzyme, wherefrom it can only be displaced by LPC and not by nucleotides. A possible dependence of severity of itch in cholestatic patients from serum LPC levels has so far not been studied, but may require attention. The crystal structure of ATX was recently resolved and these data show that the enzyme has a hydrophobic pocket that allows binding of the substrate LPC. Two N-terminal somatomedin B-like domains mediate binding of ATX to plasma membrane integrins.[22] These observations led to the view that ATX binds to the plasma membrane of target cells by way of integrin β1 or 3 and locally generates LPA, which can subsequently bind to its cognate receptors.[20]

ATX has been implicated in many (patho)biological processes including cell survival, proliferation, differentiation, and migration. ATX is involved in vascular and neural development, wound healing, and neuropathic pain, but also cancer development.

Serum ATX activity and ATX protein levels were markedly higher in cholestatic patients with pruritus than in cholestatic patients without pruritus, which were in turn higher than in healthy volunteers.[15] Serum ATX activity was also higher than in patients with pruritus due to chronic kidney disease, Hodgkin's disease, or atopic dermatitis, suggesting that serum ATX elevation is rather specific for cholestatic itch.[23] It is important to note, however, that patients with Hodgkin's disease as well as patients with atopic dermatitis have significantly elevated ATX levels in blood, although this could not be correlated to the extent of itch.[23] A role in other forms of pruritus, therefore, cannot be excluded. In these conditions local ATX production could be more important than systemic levels.

In cholestasis, serum ATX activity, but not other putative markers of itch such as serum bile salt levels or serum μ-opioid activity, were correlated with itch intensity.[15] Notably, ATX serum activity mirrored treatment response of therapeutic interventions such as the anion exchange resin, colesevelam, the potent pregnane X receptor (PXR) agonist, rifampicin, nasobiliary drainage, or MARS treatment.[23] Rifampicin was found to reduce ATX expression at the transcriptional level in human liver-derived cell lines by a PXR-dependent mechanism, possibly explaining the strong antipruritic effect of rifampicin in clinical practice,[1] at least in part.[23]

Table 2. Pros and Cons for Candidate Pruritogens in Cholestatic Pruritus

Substance	Pros	Cons	Comment
Bile salts	• serum bile salts are increased in cholestasis • experimental induction of pruritus by application of bile salts onto blister bases or keratin-stripped human skin • some antipruritic effect of anion exchange resins	• no correlation between itch intensity and serum/skin tissue concentrations of bile salt levels in cholestatic patients • women with ICP per definition suffer from itch, while bile salt levels often are only mildly increased • increased serum bile salts in asymptomatic pregnant women • effect of bile salt sequestrant colesevelam does not exceed placebo effect • itch relief after rifampicin treatment, nasobiliary drainage and extracorporeal albumin dialysis does not correlate with serum bile salt levels	Not the pruritogen searched for
Endogenous opioids	• plasma opioid levels are increased in a few cholestatic patients • μ-opioid antagonists moderately improve pruritus • opioids can cause pruritus mainly upon spinal / epidural application • Spinally administered plasma extracts of pruritic cholestatic patients induce facial scratching in monekys which was reduced by naloxone	• no correlation between itch intensity and plasma concentrations of endogenous opioids • endogenous opioids are increased in advanced stages of PBC, while pruritus is typically seen during early stages • μ-opioid activity not increased in ICP compared to pregnant controls • antinociceptive effect of cholestasis in mice is mediated peripherally, not centrally	Modulation of itch perception possible, but not causative agent
Histamine	• key pruritogen of allergic reactions • histamine concentrations are increased in plasma of cholestatic patients	• histamine-induced skin lesion are lacking in patients suffering from cholestatic pruritus • no correlation between severity of itch and histamine concentrations • antihistamines are mostly ineffective	Highly unlikely to play a causative role in cholestatic pruritus
Serotonin	• serotonin can cause itching upon intradermal application • mild beneficial effects of selective serotonin re-uptake inhibitors	• no correlation between itch intensity and serotonin levels reported so far	Modulation of itch signaling possible, but not causative agent
Progesterones and estrogens	• urinary levels of disulphated progesterone metabolites correlated slightly with the UDCA-induced improvement of pruritus in women with ICP • female PBC/PSC patients complained more about pruritus compared to male counterparts • various steroids including sulfated ones have a modulatory (stimulating) effect on the GABA receptor which in turn inhibits pain (and thus may stimulate itch) • female mice display higher scratching activity compared to male mice		Modulation of itch signaling possible; in ICP even causative role possible
Lysophosphatidic acid (LPA)	• increased levels in cholestatic patients with pruritus • intradermal application induces dose-dependent scratching behaviour in mice • activity of the LPA-producing enzyme autotaxin correlated with itch intensity • autotaxin activity closely correlated with therapeutic interventions in cholestatic patients	• LPA-receptor blockers and autotaxin inhibitors yet unavailable to test for anti-pruritic effects	The putative pruritogen in cholestasis

Although the identification of the ATX-LPA-axis as a key factor in cholestatic pruritus represents a real opportunity for development of causal therapy, several questions remain to be answered. The source of circulating levels of ATX has not been identified so far. ATX expression on messenger RNA (mRNA) levels

could be determined in various tissues and organs such as brain, adipose tissue, lung, liver, intestine, kidney, ovary, and high endothelial venules.[24] Which of these organs contribute to the circulating ATX levels being present in human plasma and cerebrospinal fluid has so far not been established. Preliminary evidence from our lab suggests that the human small intestine may be a major contributor (Bolier et al., in preparation). ATX seems to be cleared from plasma at least in part by scavenger receptors on liver sinusoidal endothelial cells.[25] ATX is not secreted into bile.[15] However, when the enterohepatic circulation is interrupted by nasobiliary drainage, circulating levels of ATX rapidly dropped concomitant with relief of pruritus,[15,23] indicating that a factor within the enterohepatic circulation is responsible for the increased ATX levels. Steroid hormones may be one of the classes of compounds that cause induction of ATX expression. Autotaxin (Enpp2) expression is upregulated in the hippocampus of ovariectomized rats upon treatment with estrogen.[26] We have observed that healthy female individuals have significantly increased serum ATX levels when using oral contraceptives (Kremer et al., in preparation). Hence, induction of ATX by estrogens appears relevant and may particularly play a role in pregnancy. It could, however, also explain the higher frequency of itch in cholestatic female versus male patients.

ATX expression is augmented upon treatment with cytokines such as tumor necrosis factor alpha (TNF-α) or interleukin (IL)-6 or growth factors such as epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF), whereas expression is reduced by interferon-gamma (IFNγ), IL-1, and IL-4.[27] It is possible that inflammatory cytokines contribute to increased serum ATX levels during cholestasis,[28] although in other states of inflammatory cytokine release pruritus is not a typical symptom. Clearly, it is at present unsolved which compound(s) in the enterohepatic circulation may be responsible for direct or indirect induction of ATX expression.

A further unsolved issue is the activation of itch-selective neurons by LPA. At present, six G-protein-coupled receptors for LPA ($LPA_{1\text{-}6}$) have been well defined. These receptors are found in various tissues including the nervous system. LPA receptors are also present on peripheral sensory neurons that mediate various sensations to the central nervous system. LPA is capable of inducing neuropathic pain by way of LPA_1-, LPA_3-, and LPA_5-receptors.[29] Recently, it was suggested that LPA may also directly activate the ion channel TRPV1 (see above).[8] Which LPA-receptor and intracellular signaling pathways are required for LPA-induced pruritus warrants further studies using small molecule inhibitors and knockout animals.

One further issue is the paradox that ATX elevation can also occur in a number of noncholestatic physiological states such as regular pregnancy and pathophysiological conditions including various cancer entities in which pruritus is not a clinical feature. Thus, other cholestatic factors may also play a role in the initiation and/or potentiation of pruritus of cholestasis. These substances may bind to certain G-protein-coupled receptors (GPCRs) such as the recently described Mrgprs on sensory neurons which are involved in itch signaling. Further screening of molecules binding to such itch-selective receptors will help to elucidate these cofactors.

Serum Bile Salts

Notably, Alemi et al.[30] recently postulated that the G-protein-coupled bile salt receptor TGR5 may play a role in the generation of cholestatic itch. They showed that TGR5 is expressed on neurons in the dorsal root ganglia of mice and this expression partially overlaps with TRPV1 and GRP. They also demonstrated bile salt-induced activation of acutely dissociated mouse dorsal root ganglia neurons. Oleanolic acid, a TGR5 agonist, was also capable of activating these cells. Importantly, *in vivo* experiments in TGR5-overexpressing mice revealed an increased basal scratch activity. Intradermal injection of 25 μg deoxycholate (DCA) evoked scratch behavior in normal mice which was partly reduced in $TGR5^{-/-}$ mice and increased in the overexpressing mice. These findings would support a primary role for TGR5 in itch induction. Unfortunately, for most of the *in vitro* experiments relatively high concentrations of unconjugated DCA (up to 100 μM) were used. These concentrations are much higher than those observed in pathological conditions like PBC or ICP, which are associated with itch. In contrast, patients with PBC and ICP suffering from itch are characterized by often only moderate elevation of serum bile salt concentrations and typically a depleted DCA pool size,[31] let alone *un*conjugated DCA barely existing in serum and bile *in vivo*. Also in the *in vivo* experiments a dose of 25 μg DCA was used, which may lead to activation and degranulation of mast cells.[32] A relation between the extent of itch and the serum bile salt concentration has been investigated many times but never found.[3] However, these considerations should not minimize the importance of aspects of this study, as they do not exclude the possibility that, besides other factors, TGR5 activation may

Table 3. Therapeutic Recommendations for the Management of Pruritus in Cholestasis

Approach	Drug/Therapy	Dosage	Evidence
Evidence-based			
ICP only	Ursodeoxycholic acid (UDCA)*	10-15 mg/kg/d (po)	I/B1*
1st line	Cholestyramine	4-16 g/d (po)	II-2/B1
2nd line	Rifampicin	300-600 mg/d (po)	I/A1
3rd line	Naltrexone	50 mg/d (po)	I/B1
4th line	Sertraline	100 mg/d (po)	II-2/C2
Experimental			
	Ondansentron	4-24 mg/d (po)/4-8 mg/d (iv)	I/B2
	Phenobarbital	2-5 mg/kg/d (po)	II-1/B2
	Propofol	10-15 mg (iv bolus) 1 mg/kg/h (iv)	I/B2
	Lidocaine	100 mg/d (iv)	II-1/B2
	Dronabinol	15 mg/d (po)	II-2/C2
	Butorphanol	1-2 mg/d (in)	II-2/C2
	Phototherapy (UVB)		II-2/C2
	Bright light towards the eyes	10 000 lux 60-120 min/d	II-2/C2
	Extracorporal albumin dialysis (e.g., MARS), plasmapharesis, plasma separation and anion absorption, nasobiliary drainage, biliary diversion		II-2/B2
	Liver transplantation		III/C1

Guideline-based standard treatment of the underlying disease is presupposed and not discussed here. Except for cholestyramine, drug recommendations are "off label use." po, per oral; iv, intravenous; in, intranasal; ICP, intrahepatic cholestasis of pregnancy.

*Recommendation and evidence grade for ICP only.

Categories of evidence according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system:

Categories of evidence

I Randomized controlled trials

II-1 Controlled trials without randomization

II-2 Cohort or case-control analytic studies

II-3 Multiple time series, dramatic uncontrolled experiments

III Opinions of respected authorities, descriptive epidemiology

Evidence grading

A High quality; further research is very unlikely to change our confidence in the estimate of effect.

B Moderate quality; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

C Low quality; further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any change of estimate is uncertain.

Recommendation

1 Strong; factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.

2 Poor; variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource or consumption.

contribute to itch perception. It is well documented that neurosteroids more than bile salts may activate TGR5 in the central nervous system.

Treatment of Pruritus of Cholestasis

Treatment of pruritus in cholestasis is based on cohort studies and randomized placebo-controlled trials in mostly limited cohorts of patients with cholestatic disorders and accompanying itch (Table 3). In ICP, ursodeoxycholic acid (UDCA) has been shown in several trials to alleviate itch and improve serum liver tests most probably due to its stimulating effect on impaired hepatobiliary secretion[33] and is regarded as the first-line treatment.[1] UDCA improves impaired hepatobiliary secretion in cholestasis both at the level of the hepatocyte and cholangiocyte, at least in part by stimulating impaired insertion of apical transporters into their target membranes, thereby enhancing the secretory capacity of hepatocytes and cholangiocytes.[33] In ICP, UDCA may enhance biliary secretion not only of bile salts, but also various other cholephiles which might be related to development of pruritus. One might speculate that UDCA, by relieving the hepatocyte from accumulation of potentially harmful substances in hepatocellular cholestasis, also indirectly modulates expression patterns of signaling molecules such as chemo- and cytokines possibly related to development of pruritus. Still, the evidence for these speculations is scarce. UDCA is also used in many other cholestatic conditions, but has not been studied with regard to itch as a primary endpoint under these conditions.[1,34]

The anion exchange resin cholestyramine effectively binds a wide variety of amphiphilic molecules in the small intestinal lumen. A potential biliary factor

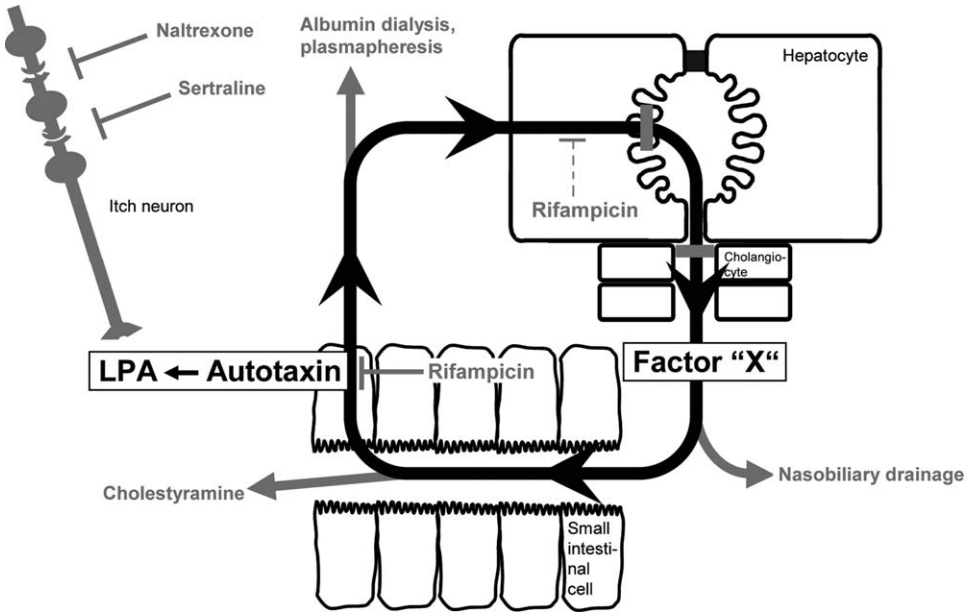

Fig. 2. Pruritogen(s) in cholestasis. Clinical observations indicate that potential pruritogens 1) accumulate in the systemic circulation (as indicated by relief of severe pruritus after treatment with plasmapheresis or albumin dialysis); 2) are secreted into bile (as proven by rapid relief of severe pruritus after nasobiliary drainage or suggested by attenuation of pruritus after administration of cholestyramine); 3) are (biotrans-)formed in liver and/or gut (as indicated by effective treatment with the potent PXR agonist, rifampicin); and 4) affect the endogenous opioidergic and serotoninergic system (as supported by the alleviating effects of naltrexone or sertraline). Recent evidence indicates that LPA formed by ATX represents a long-sought trigger of unmyelinated itch neuron endings. A biliary factor "X"[23,35] which might stimulate ATX formation remains to be unraveled.

"X,"[23,35] which may be relevant for development of cholestatic pruritus and is probably responsible for rapid relief from pruritus in PBC patients undergoing nasobiliary drainage,[36] could possibly be bound by cholestyramine in the small intestinal lumen and, thereby, be inactivated and removed (Fig. 2). In this regard, it may be relevant that ATX is expressed in the human small intestine to a considerable amount (Bolier et al., in preparation). Cholestyramine, the PXR-agonist rifampicin, the μ-opioid antagonist naltrexone, and the serotonin reuptake inhibitor sertraline are recommended by actual European and American guidelines as therapeutics and should be prescribed in a stepwise manner in order to adequately gain control over cholestatic pruritus (Table 3).[1,34] Notably, drug recommendations for treatment of pruritus in cholestasis are "off-label use" except for cholestyramine. Patients unresponsive to the evidence-based guideline-approved drugs should be referred to specialized centers to undergo experimental therapies (Table 3) such as UVB phototherapy, albumin dialysis, plasmapheresis, or nasobiliary drainage. Liver transplantation can only be regarded as the very last desperate therapeutic step, when all other measures have failed. Further unraveling of the pathogenesis of itch in cholestasis may help to develop novel, more effective strategies, among which are possibly selective ATX inhibitors and LPA receptor antagonists.

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