Neuromediators for cholestatic pruritus

Michael Duan, Hongzhen Hu

Department of Anesthesiology, The Center for the Study of Itch, Washington University School of Medicine, St. Louis, MO 63110, USA

Correspondence: Hongzhen Hu
E-mail: hongzhen.hu@wustl.edu
Received: October 07, 2016
Published online: November 14, 2016

Cholestatic pruritus is one of the most common complaints in patients with liver diseases and intra- or post-hepatic cholestasis. The mechanisms of cholestatic pruritus remain poorly understood although multiple factors are considered to participate in the pathogenesis of cholestatic pruritus. Recent exciting studies have discovered several G-protein coupled receptors (GPCRs) and endogenous chemical ligands that play critical roles in mediating cholestatic pruritus in animal models and patients. These new findings have provided novel insights into the molecular and cellular mechanisms of cholestatic pruritus and improved our understanding of the etiology and treatment for the condition.

Keywords: Cholestatic pruritus; TGR5; GPBAR1; Bile acids; farnesoid X receptor; lysophosphatidic acid; gastrin-releasing peptide; TRPA1; autotaxin


Copyright: © 2016 The Authors. Licensed under a Creative Commons Attribution 4.0 International License which allows users including authors of articles to copy and redistribute the material in any medium or format, in addition to remix, transform, and build upon the material for any purpose, even commercially, as long as the author and original source are properly cited or credited.
pruritus [5]. TGR5 was expressed by TRPV1⁺ and TRPA1⁺
dorsal root ganglion (DRG) neurons as well as neurons
expressing the itch neuromediator gastrin-releasing peptide
(GRP). Deoxycholic acid (DCA), a major bile acid, increased
the excitability of DRG neurons from wild-type but not
TGR5 knockout mice. Treatments with DCA or other bile
acids that also increase action potential firing in DRG
neurons evoked neuropeptide release from rat spinal cord and
elicted a TGR5-dependent scratching response when applied
intradermally [3]. Furthermore, pharmacological inhibition or
genetic ablation of the TRPA1 channel function prevented
the bile acid-stimulated release of pruritogenic agents and
subsequent scratching.

The nuclear receptor farnesoid X receptor (FXR), a bile
sensor extensively expressed in hepatocytes, has been
suggested to also play a role in cholestatic pruritus [6]. As part
of a detoxification system designed to shield the liver from
the adverse effects of excessive bile acids during cholestasis,
FXR activation has been shown to create or intensify pruritic
symptoms in patients with cholestasis. Cipriani et al recently
headed a study that observed the pharmacological effects of a
non-bile acid steroidal dual ligand for both FXR and
GPBAR1, BAR502, in rodent models for cholestatic pruritus.
While it was observed that injection of BAR502 induced
GPBAR1-dependent itching responses in naïve mice,
repeated challenges of the test subjects with additional doses
of the agonist were met with diminished pruritogenic
responses. In mice suffering from cholestatic conditions,
furthermore, administration of GPBAR1 agonists wholly
failed to induce itching behavior. The rapid desensitization
observed during repeated injections of GPBAR1 agonist
along with the deactivation of the itch pathway in rodent
cholestatic models seem to account for the lack of correlation
between itching severity and total bile acid concentrations in
cholestatic patients. In addition, the same experiment
revealed that the ablation of the GPBAR1 gene exacerbates
the liver damage resulting from pruritus, while the
administration of BAR502 attenuates cholestatic damage and
increases survival rates, all without inducing itch [6]. This
study suggests that the molecular agents of pruritus in
cholestatic conditions may serve vital roles in the
management of said cholestasis.

Interestingly, bile acid-elicited scratching was also
significantly reduced in mice treated with a GRP receptor
(GRP-R) antagonist or the μ-opioid receptor antagonist
naltrexone, suggesting that GRP and endogenous opioids
could be the downstream mediators of TGR5-elicited
pruritus. In fact, opioids have long been proposed as an
alternative mediator of cholestatic pruritus and naloxone has
been used to treat patients with cholestatic pruritus [7,8]. Due
to their role in the reduction of pain signaling, the release of
opioids has proven capable of inducing itch following
activation of μ-opioid receptors. While an increase in opioid
concentration has indeed been observed in cholestatic
patients, there is once again no perceived correlation between
opioid amounts and the extent of pruritus. Opioids may well
retain a role of key importance in the mechanism of
cholestatic pruritus; the ability of naltrexone and other
μ-opioid receptor antagonists to attenuate itching symptoms,
however, may also simply be explained by the intrinsic and
intimate connection between the signaling pathways of pain
and itch [9].

Recently, lysophosphatidic acid (LPA) has also been
proposed as the mediator of cholestatic pruritus based on
clinical findings that the lysophospholipase autotaxin, which
generates LPA from lysophosphatidylcholine (LPC), was
increased in sera from patients with cholestatic pruritus and
that the activity of autotaxin (ATX) in blood was correlated
with itch intensity in cholestatic patients [10]. This correlation
between autotaxin levels and itch intensity stands in stark
contrast to patterns observed with serum bile salts, where no
such relationship was present. Originally identified as a
factor in cell motility that was overexpressed in sundry
tumors and involved in the development of metastases,
autotaxin has been found to serve as a compelling indicator
of cholestatic pruritus severity and therapeutic intervention
effectiveness [11]. Patients with PBC undergoing nasobiliary
drainage treatment exhibited simultaneous decreases in itch
intensity and autotaxin activity followed by returns to
previous levels after intervention; this further evidences the
role of ATX and LPA in cholestatic pruritus [10]. Further
studies showed that serum ATX levels only increased in
patients with cholestatic pruritus but not pruritus of other
origins, such as atopic dermatitis, pruritus of uremia, or
Hodgkin’s disease. Moreover, pharmacological inhibition of
ATX activity reversibly reduced itch intensity in severe
cholestatic pruritus [10]. Intradermal injection of LPA to mice
consistently elicited a scratching response that was reduced
by antihistamines but not affected by genetic ablation of the
TGR5, suggesting distinct pathways are involved in the
generation of itch by LPA and bile acids [3, 12]. These
discoveries pave the road for the development of novel
antipruritic treatments and drugs that might function by
inhibiting ATX activity or by blocking LPA receptors.

The cellular basis of LPA-induced itch is intriguing since
LPA acts on many targets, including a 6-membered family of
GPCRs (LPA1-6) as well as the pain- and itch-sensing
TRPV1 channels [13]. LPA is a critical endogenous lipid
mediator of neuropathic pain through multiple LPA receptors including LPAR1, LPAR3, and LPAR5 \cite{14-17}. LPAR3 signaling in spinal microglia in response to nerve injury results in more production of LPA and LPAR1 signaling in schwann cells leading to myelin degradation and axon sprouting, which initiates neuropathic pain \cite{18}. Interestingly, the Aβ and Aδ but not TRPV1-positive C fibers are essential to LPA-induced neuropathic pain. On the other hand, TRPV1 expression is upregulated in the Aβ and Aδ fibers, which could contribute to the neuropathic pain response \cite{19}. Besides activation of G-protein-coupled LPA receptors, LPA was also reported to sensitize TRPV1 through LPA1/protein kinase Cε (PKCe) signaling and produce bone cancer pain \cite{20}. Additionally, Nieto-Posadas et al showed that LPA was a direct activator of TRPV1 by interacting with a C-terminal binding site of the TRPV1 to drive the channel open, which produces acute nocifensive responses \cite{13}.

Although exogenously applied bile acids and LPA can induce scratching responses, it is important to note that patients associated with cholestatic pruritus might have many more changes in the itch transduction pathway including skin, primary sensory neurons, and complex neural circuits in the spinal cord. Therefore, animal models of cholestatic pruritus are urgently needed to investigate the pathophysiology of cholestatic pruritus. Numerous studies have already been conducted which utilize naïve rodent subjects to identify mediators of the disease; the weakness of these experiments, however, lies in the fact that their conditions cannot accurately reflect the physiological environment characteristic of actual cholestatic pruritus. While artificial stimulation of protein channels may induce itch in healthy mice, this does not allow for the conclusion that the aforementioned channels are responsible for pruritic symptoms under the vastly divergent setting of a diseased system. This is directly reflected by the discrepancy between two studies focusing on the roles of TGR5 pathway in the pathogenesis of cholestatic pruritus: one study labeled the TGR5 channel as a key mediator for pruritus induced by intradermal injection of bile acids \cite{3} but the other study showed the deactivation of the TGR5 pathway in genuinely cholestatic conditions \cite{6}. It is for this reason that inquiry into the topic of cholestatic pruritus is in dire need of a shift towards cholestatic models that can authentically portray the pathophysiology present in real-world cases of the condition and away from artificial and imprecise portraits in naïve subjects. These models are, at present, scarce in rodents and virtually non-existent among mammals of other orders. New cholestatic animal models must be pioneered and developed as the next step towards uncovering the underlying mechanisms behind and mediators of cholestatic pruritus.

**Conflicting interests**

The authors have declared that no conflict of interests exist.

**Acknowledgements**

This study was partly supported by National Institute of Health grants R01GM101218 and R01DK103901, and The Center for the Study of Itch of Department of Anesthesiology at Washington University School of Medicine.

**Author contributions**

M.D. and H.H. wrote the manuscript.

**Abbreviations**

AIH: autoimmune hepatitis; ATX: autotaxin; DCA: deoxycholic acid; DRG: dorsal root ganglion; FXR: farnesoid X receptor; GPCR: G protein-coupled receptor; GRP: gastrin-releasing peptide; GRPR: GRP receptor; ICP: intrahepatic cholestasis of pregnancy; LPA: lysosphosphatidic acid; LPC: lysophosphatidylcholine; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis; PKCe: protein kinase Cε; TRPA1: transient receptor potential cation channel: member A1.

**References**


