Molecular mechanisms of pruritus in cholestasis
Kremer, Andreas

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INTRODUCTION
INTRODUCTION – AIM OF THIS THESIS

More than 350 years ago itch was defined by a German physician, Samuel Hafenreffer, as an unpleasant sensation that makes people want to scratch.¹ Nowadays chronic pruritus is defined by duration of more than 6 weeks. Chronic pruritus represents an agonizing symptom accompanying a large variety of dermatological, systemic, neurologic and psychiatric disorders.² It is commonly observed 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.³-⁵ Itching may be mild and tolerable in some patients, but may also considerably reduce quality of life, cause severe sleep deprivation, depressive mood and even suicidal ideation in more severe cases.³-⁵

Search for the potential pruritogen in cholestasis has been ongoing since 2000 years when Aretaeus the Cappadocian (1st century A.D.) stated that “pruritus in jaundiced patients is caused by prickly bilious particles”.⁵ Our state of knowledge at the start of the 21st century A.C. was not much different. In the past decades, various substances including bile salts, endogenous opioids, histamine, serotonin, or steroid metabolites have been suggested as potential pruritogens, however, a causal correlation has never been established. The aim of this thesis was to identify the real pruritogens in cholestatic liver disorders and to unravel the underlying molecular mechanisms.

The current knowledge of the molecular mechanism involved in pruritus of systemic disorders is highlighted in Chapter 2. This part of this thesis also describes in detail the signaling pathways of biogenic amines, neuropeptides, proteases, eicosanoids, cytokines, opioids, endocannabinoids, neurotrophins, phospholipids and other signaling molecules participating in pruritus. In addition, this chapter summarizes recent experimental and clinical findings focusing on the pathogenesis and current evidence-based therapeutic recommendations of pruritus in cholestatic liver disease.
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**Chapter 3** describes the identification of a potent neuronal activator in serum of pruritic patients as lysophosphatidic acid (LPA) by functional screening of sera of cholestatic patients suffering from pruritus on neuronal cells. Circulating LPA is synthesized by the lysophospholipase autotaxin (ATX) which hydrolyses the choline group from lysophosphatidylcholine. ATX levels markedly increased in sera of cholestatic patients with pruritus compared to those without pruritus. ATX activity correlated with intensity of pruritus, which was not the case for serum bile salts, histamine, tryptase, substance P or μ-opioids. Intradermally injected LPA induced dose-dependent scratch responses in mice.

**Chapter 4** highlights that increased serum ATX levels are relatively specific for pruritus of cholestasis but not pruritus of uremia and Hodgkin’s disease. Serum ATX activity closely correlated with effectiveness of therapeutic interventions including anion exchange resins, rifampicin, Molecular Adsorbents Recirculation System or nasobiliary drainage. It could be shown that the beneficial antipruritic action of rifampicin may be explained, at least partly, by PXR-dependent transcriptional inhibition of ATX expression.

In **chapter 5** we could show that serum activity of autotaxin is increased in ICP compared to other pruritic disorders of pregnancy, pre-eclampsia complicated by HELLP-syndrome, and pregnant controls. With a cut-off value of 27.0 nmol mL⁻¹ min⁻¹, autotaxin had an excellent sensitivity and specificity in diagnosing ICP from other pruritic disorders or pre-eclampsia/HELLP-syndrome. Longitudinal analysis of a subset of ICP women during pregnancy revealed a strong rise in serum autotaxin when pruritus was reported. Serum autotaxin activity was comparable in men and non-pregnant women, but increased in women taking oral contraceptives. Increased serum autotaxin during ICP was not associated with increased autotaxin mRNA in placenta.

In **chapter 6** children with cholestatic syndromes were analyzed. Serum ATX activity correlated with itch intensity in cholestatic children. Bile salts neither correlated with presence of pruritus nor increased ATX expression in vitro.

**Chapter 7** presents 13 consecutive patients with severe persistent hepatocellular secretory failure (PHSF) with deep jaundice, progressive after removal of the underlying cause (e.g., drugs, toxins, short-term mechanical biliary obstruction) and without underlying chronic
liver disease who were treated with the pregnane X receptor, rifampicin, and improved dramatically. Treatment with rifampicin resulted in relief of pruritus, serum liver tests normalized and ATX levels dropped in these patients.

In chapter 8 the results obtained in these studies are summarized and discussed in the context of the current treatment of cholestatic pruritus. LPA and ATX may form a key element of the long sought pruritogenic signaling cascade in cholestatic patients suffering from itch. 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.
REFERENCES


