Why do cholestatic patients itch?

The pruritus of cholestasis
Pruritus is a distressing symptom that often complicates the syndrome of cholestasis in patients with hepatobiliary disorders. The pruritus of cholestasis may have a severe adverse impact on a patient’s quality of life. It may not only interfere with normal activities but may lead to sleep deprivation and suicidal ideation. This form of pruritus can be an indication for liver transplantation. Gastroenterologists confronted with this problem often find themselves impotent and frustrated by the inadequacy of the options available to try and provide a patient with any substantial relief. Heroic measures (for example, charcoal haemoperfusion, partial external diversion of bile) have been tried, showing that conventional antipruritic treatments are not consistently efficacious. As long as treatments remain empirical, lacking any sound rationale based on an understanding of pathogenic mechanisms, treatment of this maddening condition will probably remain fundamentally unsatisfactory.

Cholestasis is characterised by an accumulation in plasma of substances, such as bilirubin, cholesterol, and bile acids, which under normal circumstances are efficiently secreted into bile. It has been conventional to assume that some of these retained substances are pruritogenic and that the pruritus of cholestasis arises as a consequence of an interaction between one or more of them (for example, bile acids) and nerve endings in the skin. Factors responsible for initiating pruritus in itchy skin disorders are assumed to act locally at the site of skin lesions. However, pruritus in cholestatic patients is not localised to skin lesions that may uncommonly arise as a consequence of the cholestatic process (for example, xanthomas). Indeed, the typical patient with the pruritus of cholestasis has no clinical evidence of a primary pruritic skin lesion, although secondary lesions (excoriations and prurigo nodularis caused by scratching) may develop. Furthermore, the assumption that the site of the primary event in the initiation of the pruritus of cholestasis is peripheral within the skin is not supported by convincing data.

Pruritus of central origin
It is clear from the neurological, psychiatric, and pharmacological literature that pruritus can arise centrally in the brain. As there is no evidence of any major neurological or psychiatric disorder associated with the pruritus of cholestasis, it may be pertinent to ask whether the mechanism of the pruritus of central origin to which pharmacology texts allude has any potential relevance to the pruritus of cholestasis. This mechanism seems to entail the interaction between opioid agonists, such as morphine, and opioid receptors in the central nervous system. Thus, pruritus may, in part, involve effects of opioids on neurons, since it is provoked by opioids that do not release histamine and is quickly abolished by small doses of (the opioid antagonist) naloxone and ‘central modulators of pruritus, such as systemic morphine, cause itch... by acting on central opiate receptors. Indeed, ‘itching’ has been classified as an effect of morphine on the central nervous system. The concept that opioid agonists can induce pruritus by a central mechanism is highlighted by experiments in which potent opiates were given centrally. For example, when morphine (0.2–0.5 mg/kg) was injected intracranially into cats violent facial scratching activity was induced that lasted for about 90 minutes, and when morphine (1–10 µg) (but not saline) was injected into the medullary dorsal horn of monkeys naloxone reversible facial scratching occurred. Thus, increased central opioid mediated neurotransmission/neuromodulation (opioidergic tone) induced by opiates is associated with pruritus. Accordingly, increased opioidergic tone may contribute to the pruritus of cholestasis.

The opioid system in cholestasis
Five lines of evidence have emerged which, when considered together, strongly support the concept that cholestasis is associated with increased opioidergic tone. (1) A transient reaction, which has features in common with the withdrawal of opiate addiction, has been seen after the oral administration of the potent opiate antagonist nalmefene (for example, 5 mg) to patients with chronic cholestatic liver disease. A similar reaction did not occur when high doses (for example, 300 mg) of nalmefene were given to normal subjects. (2) Analgesia (antinociception), a classic effect of opiates, occurs in an animal model of cholestasis and is reversed by (−)-naloxone (but not by its pharmacologically inert enantiomer (+)-naloxone). (3) Endogenous opioids accumulate in cholestasis. (4) Plasma extracts from patients with the pruritus of cholestasis (but not non-pruritic cholestatic controls) induce naloxone reversible facial scratching in monkeys when injected into the medullary dorsal horn, suggesting that plasma of patients with the pruritus of cholestasis contains an opioid substance that induces opioid receptor-mediated scratching activity of central origin. (5) The density of mu-opioid receptors in the brain is reduced in a model of cholestasis. Down regulation of central opioid receptors may occur in response to increased availability of endogenous opioids at opioid receptors in cholestasis.

Effects of opiate antagonists on the pruritus of cholestasis
The possibility that opiate antagonists may ameliorate the pruritus of cholestasis was first suggested by a case report published in 1979. Recently, by application of a monitoring system that objectively quantitates scratching activity independent of limb movements, mean scratching activity in eight pruritic patients with cholestasis resulting from primary biliary cirrhosis was shown in a single blinded trial to be 50% less during naloxone infusions than during placebo infusions. This effect of naloxone was subsequently confirmed by the results of a double blind placebo.
controlled trial in which 29 pruritic patients with cholestasis caused by several different liver diseases were enrolled. Furthermore, in the double-blind trial the mean value for a visual analogue score of the perception of pruritus was significantly less during naloxone infusions than during placebo infusions. Thus, both the perception of pruritus and scratching activity in patients with the pruritus of cholestasis can be ameliorated by an opioid antagonist. In contrast with naloxone, nalmefene is efficacious as an opioid antagonist when given orally. In one open label trial subjective assessments of pruritus suggested that nalmefene given orally may be associated with a sustained amelioration of pruritus in cholestatic patients. In another open label trial quantitative data on scratching activity and visual analogue scores of pruritus also suggested that oral nalmefene induced sustained beneficial effects in most patients with unrelieved pruritus secondary to cholestatic liver disease.

The validity of these inferences has been confirmed in a randomised, blinded, placebo controlled trial.

Concluding perspectives

Increased opioidergic neurotransmission/neuromodulation (tone) in the central nervous system seems to contribute to the pruritus of cholestasis. Only interactions between certain opioid peptides and certain opioid receptor subtypes may be relevant to this phenomenon. Both the nature and source of the endogenous opioid peptides involved in this pathogenic mechanism are currently unknown, but one source may be the cholestatic liver itself. The new findings implicate a specific class of substances, endogenous opioids, and abnormal neurotransmission/neuromodulation in the brain in the pathogenesis of the pruritus of cholestasis. They also provide a rationale for giving orally bioavailable opiate antagonists to obtain long-term relief from this form of pruritus. In addition, these findings make it necessary to consider the possibility that cholestasis-related changes in the opioid system may lead to changes in other neurotransmitter systems and that such secondary changes might be responsible for a contribution to the pruritus of cholestasis in addition to that from changes in the status of the opioid system alone. For example, it is conceivable that altered serotonergic neurotransmission might contribute to the pruritus of cholestasis. Like the opioid system, the serotonin system has been reported to modulate nociception (the perception of pain) in rats and, hence, may also modulate the perception of pruritus. Indeed, anecdotal reports and a placebo controlled (but not double blind) trial suggest that the 5-HT3 serotonin receptor antagonist ondansetron may ameliorate the pruritus of cholestasis. However, at the time of writing, no data that show definitively that serotonergic neurotransmission is abnormal in cholestasis have been reported.

There is currently a paucity of data that show that peripheral events (in the skin) initiate the pruritus of cholestasis. Nevertheless, a contribution to pathogenesis from neural events originating in peripheral cutaneous nerve fibres cannot be excluded. However, there is now evidence that strongly suggests that cholestasis-related abnormal neurotransmission/neuromodulation in the central nervous system plays a part in the mediation of the pruritus of cholestasis.

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