hormone in human anterior pituitary tissue and to gastrin, gastric inhibitory polypeptide, glucagon, motilin, somatostatin, secretin, and vasoactive intestinal peptide in serial sections of human upper small-intestinal mucosa. Cells reacting with prolactin antiserum were found in biopsy specimens of small-intestinal mucosa from both patients with and patients without coeliac disease. The cells were located in the crypts of Lieberkühn with occasional cells in the lateral epithelium of villi or on the luminal surface of specimens from patients with coeliac disease. The figure shows a prolactin-immunoreactive cell from the neck of a crypt in a specimen obtained from a patient without coeliac disease. It is a typical intestinal endocrine cell with a long apical process reaching to the luminal surface. Fluorescence was located fairly uniformly throughout the cells apart from the centrally located nucleus. Background fluorescence appeared to be within blood vessels rather than nerves.

Single prolactin cell in epithelium of normal human jejunal villus showing immunofluorescence. Modified Susa fixation. × 400 (original magnification).

Specificity studies on human anterior pituitary tissue showed that the prolactin antiserum stained a different population of cells from that stained by primary antisera to human growth hormone or adrenocorticotrophin hormone. In the small-intestinal mucosa prolactin staining was considerably reduced by prior incubation of Tenovus antiserum with human prolactin, whereas when gastrin, gastric inhibitory polypeptide, glucagon, motilin, secretin, somatostatin, and vasoactive intestinal peptide polypeptide were used no reduction in the intensity of fluorescence was observed. In addition, serial sections stained with primary antisera to the gastroenteropancreatic hormones showed populations of cells whose distribution or morphology or both did not correspond to the prolactin immunoreactive cells.

Comment

Using an antiserum directed against human pituitary prolactin we showed cells containing prolactin immunoreactivity in human small-intestinal mucosa. The immunoreactivity was intracellular though extracellular and was typical of that seen in other populations of cells of the intestinal endocrine system. The distribution of the staining was unlike the "internalised" prolactin seen within the Golgi apparatus of hepatocytes. The cellular distribution in the gastrointestinal tract has yet to be determined.

Isolation and characterisation of gut prolactin immunoreactivity should allow specific antibodies to be raised for radioimmunoassay and ultimate elucidation of its biology in man.

We thank Professor C F McCarthy and Professor K D Buchanan for encouragement and the Western Health Board, Ireland, for financial support.


(Accepted 23 December 1981)

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Intraspinal opiates and itching: a new reflex?

Facial itching is a common, unwelcome, and unexplained side effect of intraspinal opiates. Opiates release histamine from mast cells in body tissues, but it is not known whether histamine is wholly or even partly to blame for the itching referred so constantly and so specifically in the distribution of the trigeminal nerve. There is mounting evidence in favour of a central, enkephalinergic mechanism for some kinds of itch. Itching induced by butorphanol, a morphine-like analgesic that does not raise blood histamine concentrations, can be prevented by naloxone. Naloxone has also proved successful in the treatment of generalised itch in patients with liver disease.

We report on three patients in whom facial itching provoked by intrathecal opiate responded to intravenous naloxone.

Case reports

Two women aged 35 and 41 years were scheduled for elective cholecystectomy. Both received 1.0 mg intrathecal morphine sulphate in 0.1 ml saline isobaric with cerebrospinal fluid at the L3-L4 interspace 30 minutes before induction of general anaesthesia.

On recovery from anaesthesia two hours after receiving the intrathecal morphine the first patient scratched her nose vigorously and complained of facial itching, most pronounced in the nostrils. Naloxone 0.4 mg intravenously provided immediate, complete, and permanent relief, analgesia being unaffected.

A third patient also underwent cholecystectomy. She was given 1.0 mg diamorphine hydrochloride intrathecally and complained of facial itching five hours later. Intravenous naloxone 0.4 mg successfully abolished the itch.

Comment

Our results support the view that a central enkephalinergic component may play a part in opiate-associated itching. They do not so readily explain how intraspinal opiates consistently induce itching referred in the distribution of the trigeminal nerve. We suggest that this phenomenon may be neural in origin, the result of a spinal reflex transmitted through a medullary itch centre associated with the spinal nucleus of the trigeminal nerve.

In some animals there is evidence of a "scratch centre," which lies in the caudal part of the floor of the fourth cerebral ventricle. In man itching of the nostrils is an "absolutely specific" clue to the presence of a cerebral tumour that has infiltrated the floor of the fourth ventricle.

Like the substantia gelatinsosa of the spinal cord—where intraspinal opiates act to produce analgesia—the spinal nucleus of the trigeminal nerve is rich in opiate receptors. At the level of the third or fourth cervical segment of the cord the spinal nucleus and tract of V become continuous with and indistinguishable from the substantia gelatinsosa and the tract of Lissauer. Cells in the grey matter of the dorsal horn have further, indirect access to both trigeminal nuclei by spinotrigeminal interneurones that travel in the antrolateral quadrant of the cord (D Bowsher, personal communication). These might be
potential routes for a multisynaptic itch reflex from the substantia to the nucleus of the trigeminal nerve in the medulla.

The transmission of nerve impulses that give rise to a spinal reflex may be blocked by local anaesthesia. Our patients have not complained of itch since we added a small amount of bupivacaine to our intrathecal heroin preparation (1·0 mg freebase-dried heroin and 0·25 mg bupivacaine plain in 1·0 ml saline; pH 6.183, specific gravity 1.004 at 37°C).

On this evidence an enkephaline reflex may well provide a credible alternative to histamine release as an explanation for facial itching associated with intraspinal administration of opiates. The reflex might be relayed at a central level by a medullary itch centre having a close functional link with the spinal nucleus of the trigeminal nerve.

We thank Dr J A Savin, Royal Infirmary, Edinburgh, and Dr I Parkin, Medical School, Birmingham, for key references.

Acute pancreatitis: a complication of beta-blockade

Severe hypertriglyceridaemia is a well-recognised cause of acute pancreatitis. Increases in serum triglyceride concentration have been reported after beta-adrenergic blockade.1-4 We describe a patient in whom beta-blockade was associated with severe hypertriglyceridaemia and acute pancreatitis and in whom beta-blocking agents were shown to impair serum triglyceride clearance.

Case report

A 64-year-old man with a 20-year history of peripheral and coronary artery disease was admitted as an emergency case because of prolonged angina at rest. He was not diabetic and drank alcohol only occasionally. He had been prescribed metoprolol 100 mg twice daily but on admission had a sinus tachycardia (130 beats/min). Propranolol 5 mg intravenously relieved his angina and reduced the heart rate, and atenolol 100 mg by mouth was started.

On the fifth hospital day the laboratory was unable to perform routine biochemical tests because of pronounced turbidity of the serum. Concentration of serum triglycerides was 56·0 mmol/l (4956 mg/100 ml) (normal < 1·7 mmol/l (150 mg/100 ml)) and of serum cholesterol 18·0 mmol/l (695 mg/100 ml) (normal < 7·0 mmol/l (270 mg/100 ml)). Type V hyperlipoproteinaemia was confirmed by ultracentrifugation. Before admission serum triglyceride values had been raised during metoprolol treatment, but had not exceeded 13 mmol/l (1150 mg/100 ml). Next day the patient developed back pain and two days later severe central abdominal pain and hypotension. Serum amylase activity was 4460 U/l, confirming acute pancreatitis. There was no clinical evidence of intestinal obstruction, and abdominal radiography and ulcerological examination showed no free gas or gall stones. He was managed conservatively with intravenous fluids and nasogastric aspiration. As he improved a diet containing 20 g fat was introduced. An attempt to withdraw beta-blocking drugs failed because of recurring angina and tachycardia. Despite this, the low-fat diet the concentration of serum triglycerides was down to 3·7 mmol/l (327 mg/100 ml) and cholesterol to 7·0 mmol/l (270 mg/100 ml) within two weeks.

The patient was subsequently admitted to the medical ward and, while continuing a 20 g fat diet, the effect of atenolol 100 mg daily and metoprolol 100 mg twice daily on the clearance of intravenously administered 10% Intralipid (1·0 ml/kg) was studied.5 In the absence of beta-blockade triglyceride clearance was normal, but was almost halved by both beta-blockers (figure).

Comment

The rise in concentration of serum free fatty acids which occurs with stress may result in increased hepatic production of triglycerides. Such stress-induced hypertriglyceridaemia is not, however, enough to cause acute pancreatitis and, in any case, beta-blockade reduces serum free fatty acid concentrations6 and would thus limit hypertriglyceridaemia from this cause.

The rise in the concentration of serum triglycerides in our patient was apparently due to impaired catabolism, since beta-blockade was associated with impaired triglyceride clearance. This most probably reflected reduced endothelial lipoprotein lipase (EC 3.1.1.3) activity. Lipoprotein lipase removes triglycerides from both chylomicrons and very low density lipoproteins. It has been suggested that alpha-adrenergic stimulation, unopposed by beta-adrenergic stimulation, reduces the activity of this enzyme7 and that this may be the mechanism by which beta-blocking drugs, in particular those without beta-agonist (intrinsic sympathetic) activity, permit impairment of triglyceride clearance. In stress, when catecholamine secretion is increased, such an effect would be heightened. We suggest that the stress of acute myocardial ischaemia in the presence of effective beta-blockade so impaired triglyceride clearance in our patient that serum triglyceride concentrations sufficient to provoke acute pancreatitis were achieved.

Doctors prescribing beta-blockers for acute coronary insufficiency should be alert to the possibility of inducing severe hypertriglyceridaemia in susceptible patients and its dangerous complication.

We thank Professor S W Stanbury for permission to study this patient.

References


(Accepted 14 December 1981)

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