Stress and Acute Biliary Pancreatitis

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According to Selye’s [1] classic work, the general adaptation syndrome in response to stress involves a complex neurohumoral regulation: the release of ACTH and corticosteroids combined with catecholamine discharges and other factors resulting in gastric ulcerations because of disequilibrium between aggressive and defensive (cytoprotective) mechanisms. Overstimulation of these factors may worsen some diseases such as acute biliary pancreatitis, which per se is a stressful situation that disturbs biliary-pancreatic outflow and the autonomous nervous system as well as duodenopancreatic feedback regulation. Indeed, stress-induced gastric and duodenal ulceration is frequent in acute biliary pancreatitis with severe cholangitis, although the literature about the frequency of stress ulcers caused by an acute pancreatitis is rare and mostly of older date [2]. A combination of the two situations can worsen the outcome of biliary pancreatitis, as was demonstrated by the extensive experimental work of Cosen-Binker et al. in this issue of Pancreatology. However, short-term stress induction before pancreatitis did not worsen but slightly ameliorated the severity parameters of the inflammatory process in parallel to increasing serum corticosterone levels. Recovery from stress situation releases a group of acute-phase proteins such as heat shock proteins (HSPs), represented by HSP72 in this study. These are highly conserved, ubiquitous and functionally related proteins that play an essential part in cell survival. Following stress conditions, many cellular proteins become partially or completely denatured or malfolded. HSPs recognize this, bind to the damaged proteins and stabilize and refold them.

Cells subjected to a mild, sublethal stress event sufficient to increase the levels of HSPs are able to survive a subsequent more serious stress event. HSP preinduction is known to protect the pancreas against cerulein-induced pancreatitis in rats [3]. Water immersion pretreatment and possibly HSP60 and HSP72 exert a definite protective effect in mild pancreatitis, but this was not seen in more severe acute pancreatitis models [4]. Timing of stress induction is important to achieve the beneficial effect of HSPs as demonstrated by the experiments of Cosen-Binker et al. (experiments 21–24): when animals underwent the same short-term stress after the acute biliary pancreatitis had been completed, all of them died between 5 and 8 h after the ‘bilio-pancreatic-duct outlet exclusion-closed duodenal loop’ maneuver. This fact points to the clinical relevance of HSP induction treatment and also underlines the multifactorial nature of progressive biliary pancreatitis (for instance, autoactivation of pancreatic enzymes, proinflammatory cytokines, oxidative stress, microcirculatory damage). In this situation a mild stress induction cannot prevent but will definitely deteriorate the inflammatory process. A previous stimulation with medium- and long-term stress induction was associated with more severe acute pancreatitis and more severe hemorrhagic ulcerations in the stomach. The au-
thors demonstrated the most important factors involved in the stress-induced deterioration of pancreatitis and gastric ulcerations. Cholinergic stimulation and CCK release seem to be of minor importance as specific receptor blockade resulted in only insignificant amelioration of the pancreatitis; the gastric ulcerations even worsened with the anti-CCK treatment. A local anesthetic applied outside and inside of the periampullary region after stress induction but before provoking acute biliary pancreatitis significantly ameliorated the severity indicators as well as the histopathological findings. Similar results were achieved with a combined α and β adrenergic blockade. The two mechanisms were additive. The beneficial effect of local anesthesia at the periampullary region can be explained by interruption of autonomous arc reflexes, implicated in the gastric and pancreatic physiology by Tiscornia et al. [5] and Debas and Yamagishi [6]. Moreover, it has been well demonstrated that periampullary anesthesia inhibits interdigestive gastrointestinal motility through gastric and pancreatic secretions [7]. This treatment spares the pancreas and stomach, thus increasing the chances for recovery from gastric ulcerations and pancreatitis. Another factor involved in the long-term restraint stress might be the release of catecholamines due to overstimulation of the sympathetic nervous system and the pituitary-supra-adrenal axis as a consequence of the long-lasting alarm reaction, resulting in a depletion of endogenous glucocorticoids [1] and microcirculatory disturbances. Visceral hypersensibility due to catecholamine discharges from the afferent visceral fibers leading to increased intrapancreatic cholinergic tone with exaggerated response to CCK is not supported by the insignificant effect of atropine and a CCK antagonist in these experiments and in clinical practice.

Use of local anesthesia at the periamplular region with or without sympathetic blockade seems to be worthwhile to test in a well-controlled clinical study. Lechin et al. [8] reported on 5 patients with acute pancreatitis resistant to conventional treatment who improved dramatically with clonidin. All of them showed elevated plasma levels of adrenalin, noradrenalin and cortisol as stress indicators, which decreased abruptly after initiation of clonidin therapy. Acute biliary pancreatitis in humans is triggered by complex stressful situations caused by abdominal pain, meteorism and jaundice, and leads to hospital admission, clinical investigations, restriction of food and endoscopic retrograde cholangiography. Controversial results of endoscopic papillotomy in acute biliary pancreatitis may be explained by stress situations in inexperienced, low-volume institutions of multicenter studies [9]. The use of local anesthesia at the periampullary region before papillotomy seems to be feasible as almost all of the previous measures to prevent post-ERCP pancreatitis have failed [10]. However, early papillotomy with jejunal feeding [11] and optimal intensive care remain the treatment of choice, which could be supplemented with topical anesthesia and sympathetic blockade if well-controlled clinical trials were to confirm the results of the animal experiments.

References