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Nitric Oxide Pathways and Evidence-Based Perturbations in Acute Pancreatitis

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Key Words
Nitric oxide · Nitric oxide synthase · Acute pancreatitis · Endoscopic retrograde cholangiopancreatography · Chemoprevention

Abstract
Nitric oxide (NO) is a gaseous neurotransmitter, a vasodilator and paracrine regulator. In the pancreas, NO regulates normal pancreatic exocrine secretion, endocrine pancreatic insulin secretion and pancreatic microvascular blood flow. NO has multiple species and is produced de novo by 3 NO synthase enzymes. Endothelial NO synthase reduces the severity of the initial phase of experimental acute pancreatitis (AP). Cigarette smoking and chronic alcohol use disrupt normal NO pathways and are associated with pancreatitis and pancreatic cancer. The aims of this minireview are to describe normal intrapancreatic NO pathways, perturbations during experimental AP and due to epidemiological factors associated with pancreatic pathology, and the clinical implications of NO on AP.

Nitric Oxide Synthase Isoforms and Pathways in the Pancreas

Nitric oxide (NO) has complex and sometimes paradoxical biological effects, acting as a regulatory/anti-inflammatory mediator and as a cytotoxic/proinflammatory agent [1]. NO's biological function is influenced by the specific NOS isoform involved in NO synthesis, the location of NO production, and the amount of NO produced [2]. De novo synthesis of NO arises from 1 of 3 NO synthase (NOS) isoforms, each named for their initial localization in vascular endothelium (eNOS), neurons (nNOS) and macrophages (iNOS) [2]. For this reason, mice with genetic deletion of individual NOS isoforms [3–5] are invaluable tools for defining the biological role of each NOS.

In the pancreas, eNOS and nNOS are constitutively expressed in the vasculature and in neurons, respectively, and acini weakly express eNOS [6]. eNOS and nNOS are calcium-dependent enzymes with a low-level NO output, contrasting with iNOS, which is calcium insensitive and has a high NO output. Direct measurement of pancreatic nitrite/nitrate production (an indicator of NOS activity) is confounded because NO production is the sum pro-

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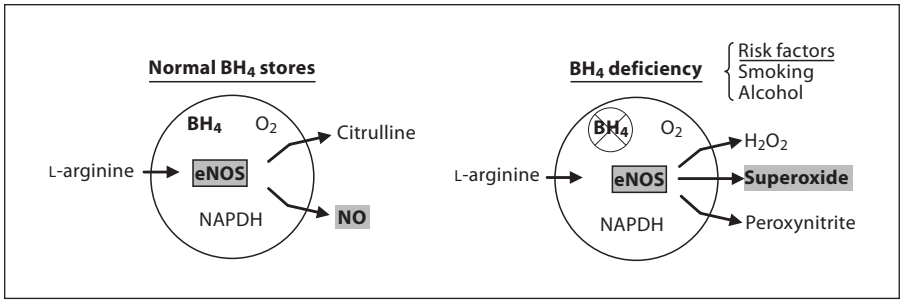

Fig. 1. BH_4 deficiency uncouples eNOS from NO production.

duced by eNOS and nNOS. Central to our recent studies [6], regulation of eNOS enzyme activity is heavily influenced by changes in eNOS phosphorylation and post-transcriptional processes that influence mRNA stability (such as lipopolysaccharide, cytokines and hypoxia).

To further understand how eNOS signal complex assembly and membrane association mitigates eNOS phosphorylation events [6], we investigated the stabilization of the dimeric eNOS signaling complex by the reduced pteridine tetrahydrobiopterin (BH_4). Functionally, BH_4 couples eNOS enzyme activity to NO synthesis, whereas BH_4 deficiency shifts the output of eNOS enzyme activity away from NO in favor of superoxide and oxidative stress [7], causing endothelial dysfunction (fig. 1). A major cause of endothelial dysfunction is BH_4 depletion by cigarette smoking [8–10] and alcohol consumption [7], major risk factors for pancreatic pathology. Impaired NO production by eNOS occurs early in the development of vascular diseases, including diabetes, hypertension, atherosclerosis, myocardial or cerebral ischemia and possibly pancreatic diseases. Experimentally, evidence for this relationship exists as mice with an eNOS gene deletion have hypertension, insulin resistance and enhanced myocardial or cerebral tissue injury to ischemia-reperfusion injury. Also, in cross-sectional or case-control genetic studies, populations with vascular diseases have an increased incidence of eNOS gene polymorphisms.

NOS in Experimental Pancreatitis and Associated Pathophysiology

NO has a controversial role in experimental acute pancreatitis (AP). In some studies NO had a protective effect [11, 12], possibly by increasing pancreatic microvascular blood flow (PMBF), but in other studies it had no effect [13] or a deleterious effect [14, 15], the latter possibly due to oxidative stress [14] or vasodilation and organ hypoperfusion [15]. To clarify the effect of NO on experimental AP, we and others recently used pharmacologic inhibition or genetic deletion of individual NOS isoforms in mice. Two groups reported conflicting effects of iNOS gene deletion on the late inflammatory phase of caerulein-induced AP in mice; iNOS gene deletion was protective in one study [16] and injurious in the other [17]. We found that during the initiation of caerulein-induced AP, eNOS-derived NO reduced the disease severity and other NOS isoforms had no effect [6]. This protection may be related to eNOS maintaining pancreatic exocrine secretion of activated enzymes as we recently showed that non-selective NOS inhibition or eNOS gene deletion reduced CCK-8 and carbachol-stimulated pancreatic secretion by ~50% [18].

A likely second factor is that NO modulates PMBF; eNOS localizes to the vasculature [6] and during induction of AP in WT mice, eNOS becomes dephosphorylated (an indicator of eNOS activation) and PMBF increases by 178%, an effect abolished by eNOS gene deletion [6]. Others reported also that the severity of AP correlates inversely with PMBF in human [19] and experimental [20, 21] AP; PMBF decreases in severe, necrotizing AP but increases in mild, edematous AP [20, 21]. Because eNOS regulates organ blood perfusion [2] and is a peripheral chemoreceptor for hypoxia [22], we proposed that eNOS may trigger PMBF augmentation to maintain oxygen delivery or extraction for cell metabolism and to clear injurious by-products of metabolic processes.

The benefits of augmenting local eNOS-derived NO during AP may depend on coexisting eNOS dysfunction. First, pancreatic eNOS protein expression does not change during early and inflammatory phases of AP [6]. Secondly, we anticipated that AP in normal mice would lead to BH_4 oxidation and endothelial dysfunction. Surprisingly, we found that mice with AP had a 5-fold increase over baseline in pancreatic tissue BH_4 concentrations (quantitated by an HPLC fluorescence method [9]) and a

parallel 2.5-fold increase in pancreatic tissue mRNA expression of GTP cyclohydrolase I (NM_008102), the latter being responsible for de novo BH_4 synthesis [DiMagno et al., unpubl. data]. Because of excess pancreatic BH_4 present during AP, supplemental BH_4 is unlikely to further augment eNOS coupling to NO, as recently questioned [23], and may not be effective pharmacotherapy for AP except in conditions associated with decreased BH_4 bioavailability such as smokers and/or drinkers with AP (see below).

Epidemiological Factors Associated with Pancreatic Pathology Perturb NOS Pathways

Why cigarette smoking and chronic alcohol consumption have broad effects on pancreatic physiology and pathophysiology is unclear. Cigarette smoking alters pancreatic secretion [24] and increases the risk of developing acute [25, 26] and chronic [25–27] alcoholic pancreatitis, idiopathic chronic pancreatitis [26], pancreatic calcifications in late-onset but not early-onset idiopathic chronic pancreatitis [28], and pancreatic cancer [29]. Further, smoking accelerates the progression of alcoholic chronic pancreatitis [27] and late-onset but not early-onset idiopathic chronic pancreatitis [30]. An important interaction among calcification, smoking and alcohol ingestion is that calcifications occurred more frequently in smokers and correlated with the amount and duration of drinking [31–33]. Finally, exposures to cigarette smoking and likely alcohol consumption contribute to cardiovascular disease, which is the leading cause of death in patients with alcoholic chronic pancreatitis.

As illustrated in figure 1, the development of BH_4 depletion and endothelial dysfunction may be the common pathway leading to pancreatic pathology by cigarette smoke and alcohol. In humans, chronic smoking reduces endothelium-dependent vasorelaxation, primarily due to BH_4 depletion and eNOS dysfunction rather than to cigarette smoke-induced elevations in reactive oxygen species [10]. BH_4 supplementation restores the vasodilatory response in chronic smokers, who have reduced forearm blood flow evoked by acetylcholine. Antioxidant effects of BH_4 do not explain these observations because a chemically related pteridine family member, tetrahydroneopterin, has antioxidant properties but no effect on the vasodilatory response in smokers because it cannot couple eNOS to NO synthesis. Recent in vitro studies aimed at chemically identifying the NOS inactivator(s) in cigarettes and cigarette smoke showed that extract prepared from cigarette smoke or unsmoked, ground cigarettes (but not nicotine) irreversibly inhibited nNOS activity by suicide inactivation and reversibly inhibited eNOS enzyme activity by depleting BH_4 within 30–60 min, but nicotine had no effect [9]. Relevant to the pancreas, nNOS inactivation may disrupt neural-mediated smooth muscle relaxation of gastrointestinal tract sphincter muscles, including the sphincter of Oddi, and pose a risk for pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP). Further, because acute exposure to cigarette smoke is sufficient to impair eNOS activity, it is tempting to speculate that BH_4 deficiency is responsible for findings in an experimental model of alcoholic AP; acute cigarette smoke exposure reduced PMBF and potentiated acute pancreatic injury in rodents [34]. For clarification, experimental and clinical studies are required.

Potential Clinical Application of NO in AP, Including ERCP Trials

NO excess or deficiency may contribute to pancreatic and systemic pathology. This section addresses two questions. Do systemic NO levels predict severe AP? Does supplemental NO reduce the incidence of post-ERCP AP?

Excess NO. Two studies with severe AP patients reported that systemic NO levels increased and correlated with the severity of AP [35, 36], but only one study included a control group with mild AP [36]. The validity of this latter study is unclear because the increase in blood of reactive NO species 72 h after onset of abdominal pain correlated with severe AP based only on the Atlanta criteria but not based on C-reactive protein levels or 48-hour Apache II scores [36]. As further evidence that systemic NO increases only slightly in mild nonalcoholic AP, the NOS substrate L-arginine (fig. 1) was depleted and urine NO was low in patients with predominantly mild AP 24 h after admission. For unexplained reasons, alcoholics with AP compared to those without AP had lower serum L-arginine values but similar urine NO concentrations [37]. Additional studies are required to define the relationship between systemic NO levels and AP severity.

Supplemental NO. NO and other pharmacological agents have no proven effect on post-ERCP AP [38] but have been used to reduce/prevent intrapancreatic protease activation, inflammatory cytokine generation and pancreatic sphincter of Oddi hypertension, a known risk factor of post-ERCP pancreatitis [39]. Most ERCP studies

Table 1. GTN and post-ERCP pancreatitis: comparisons of 3 randomized controlled trials

Study variables	Moreto et al. [47]	Sudhindran et al. [46]	Kaffes et al. [48]
Pharmacology			
GTN dose	15 mg/24 h	2 mg	5 mg/24 h
Route of GTN delivery	transdermal	sublingual	transdermal
GTN delivery	3.75 mg/6 h	2 mg/6 h	1.25 mg/24 h
Duration of GTN effect, h	24	6	24
Institutional			
Background rate of post-ERCP pancreatitis, %	15	18	8
Endoscopists, n	2	1	2
Population[1]			
Study population size, n	140	186	318
Mean age, years	67 vs. 65	64 vs. 64	60 vs. 65
Female, %	62 vs. 59	76 vs. 62	62 vs. 65
Suspected sphincter of Oddi dysfunction, %	3 vs. 3	NA	23 vs. 12
Previous history of post-ERCP pancreatitis, %	NA	NA	1.9 vs. 1.8
Previous history of pancreatitis, %	NA	20 vs. 15	16.1 vs. 21.5
Alcohol abuse, %	13 vs. 8	NA	NA
Smoking	NA	NA	NA
Technical			
Prophylactic pancreatic duct stenting	no	yes	yes
Cannulation rate (GTN vs. placebo), %	99 vs. 97	93 vs. 92	97 vs. 99
Endoscopic sphincterotomy (GTN vs. placebo), %	59 vs. 56	30 vs. 22	NA
Outcome			
Incidence of post-ERCP pancreatitis (GTN vs. placebo), %	4.2 vs. 15.1	7.8 vs. 17.7	7.7 vs. 7.4
Severe AP, n	1	0	0
Mortality, n	1	0	0

[1] Data are presented as GTN versus control group. NA = Not available.

enrolled patients with a low-average risk (~5%) rather than a high risk (>10%) of post-ERCP AP, even though a discernable effect of pharmacotherapy may be greatest in patients at high risk of post-ERCP pancreatitis, defined by preprocedural factors (age, gender, suspicion of sphincter of Oddi dysfunction) and procedural factors (number of cannulation attempts, rapidity of pancreatic duct emptying of injected contrast). Currently, the only proven risk-reducing intervention for post-ERCP pancreatitis is prophylactic pancreatic duct stenting in high-risk groups [40], intended to prevent ductal outflow obstruction. Because prophylactically stenting the pancreatic duct is not universally protective and may increase the risk for AP, selecting patients with sufficient risk to warrant prophylactic stenting is a major challenge.

Pancreatic duct outlet obstruction might also be prevented by pharmacological measures that relax the periampullary sphincter, such as botulinum toxin [41], calcium channel blockers [42, 43] and the NO donor glyceryl trinitrate (GTN) [44, 45]. In randomized controlled trials of post-ERCP AP of oral or topically applied agents, nifedipine had no effect on the incidence of AP [42, 43] and GTN reduced the incidence [46, 47] or had no effect [48]. The conflicting findings in the GTN studies are attributable to multiple factors (table 1). The GTN studies had similar age and gender distributions, used comparable criteria for diagnosing post-ERCP AP, achieved similar ERCP cannulation rates, and had a negligible frequency of severe AP. In contrast, major differences among the GTN studies included the drug dose, route of delivery, timing of administration and duration of treatment, the institutional background rate of post-ERCP AP, the percentage of patients with suspected sphincter of Oddi dysfunction and the use of prophylactic pancreatic duct stenting in high-risk patients. Unfortunately, data are lacking to compare exposures to smoking and alcohol abuse, which are risk factors for endothelial dysfunction and potentially high-risk characteristics that would predict which subjects would benefit from GTN.

Conclusion

Excess or deficient NO may have untoward repercussions in the pancreas. Because of the likely pathophysiological role of NO in AP, it is possible but unproven that NO-related pharmacotherapy may prevent or ameliorate AP. A novel hypothesis is that cigarette smoking or alcohol consumption may increase the incidence or severity of AP by uncoupling eNOS from NO production (endothelial dysfunction). There is insufficient data to conclude whether prophylactic GTN treatment reduces the incidence of post-ERCP AP. Whether populations with endothelial dysfunction would preferentially benefit from GTN to reduce the incidence of post-ERCP AP requires further study.

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