Mini Review

Inflammation and incretins

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ABSTRACT

Nutrient excess results in systemic inflammation in diabetes contributing to insulin resistance, dyslipidaemia and increased cardiovascular risk. GLP-1 agonists and DPP-4 inhibitors, which are now well accepted therapies for diabetes may play a unique role in modulating this inflammatory process. Incretin based therapies have shown beneficial anti-inflammatory effects on surrogate markers but cardiovascular outcome data is still lacking.

Key words: Inflammation, diabetes, GLP-1 agonist, DPP-4 inhibitor

The preceding two decades have witnessed a near exponential development of an entirely new modality of treating diabetes mellitus: The incretin-based therapy. The basis of this is the so-called incretin effect, which consists of a greater insulin response to oral glucose as compared to that with IV glucose under euglycemic conditions. The two principal mediators of the incretin effect are the gut hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide GLP-1.

The demonstration in type 2 diabetes mellitus of a deficiency of GLP-1 secretion or action has led to the development of the incretin or GLP-1-based therapy, which involves using either a GLP-1 receptor agonist like exenatide or increasing the endogenous GLP-1 levels by preventing its degradation by DPP-4 through specific inhibitors of this enzyme.

There is now a large body of evidence to establish the efficacy and (relative) safety of such GLP-1-based agents in the treatment of T2DM. This is largely based upon the ability of these agents to lower HbA1c levels through various mechanisms. Interest, however, has aroused from the pleotropic effects of these agents, among which the effect of incretins/GLP-1 on inflammation will be the subject of this mini review.

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What has Inflammation got to do with diabetes?

Inflammation is the survival response of an organism when challenged with infection, injury, or toxins. In the classic sense, inflammation is limited to the tissue involved (tissue inflammation), is mediated by the innate immune response initiated by the toll-like receptor (TLR), and should subside once the insult has been overcome. However, if the insult continues to persist, as in nutrient or metabolite excess, low-grade inflammation always remains turned on with activation of the adaptive immune response, resulting in what we now know as systemic inflammation. Such inflammation can be mediated by cytokines like TNF-α, hormones such as leptin, lipids themselves, endoplasmic reticulum (ER) stress, and ROS production because of glucose excess, and is identifiable by markers such as CRP and IL-10, which are elevated in diabetes and obesity.

The inflammatory response is an energy requiring process; hence inflammatory and immune pathways are closely linked with metabolic pathways, one always influencing the other, and both often utilizing the same signaling proteins and transcription factors (TFs). Inflammatory processes require a catabolic rather than an anabolic response and, therefore, lead to suppression of the insulin signaling (insulin resistance). Nutrient excess leading to a chronic metabolic overload is now well-established as a source of

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chronic systemic inflammation in obesity-linked diseases like T2DM, atherosclerosis, non-alcoholic fatty liver disease (NAFLD), and airway inflammation.[1]

Activation of inflammatory pathways leads to activation of serine/threonine kinases such as JNK, which suppresses insulin signaling on one hand, and activates pro-inflammatory proteins such as activator protein-1 (AP-1) on the other. Another kinase activated is IKK, or inhibitor of NFkB kinase, that leads to activation of NFkB. Both AP-1 and NFkB induce transcription of several pro-inflammatory genes. SOCS3 is another signaling protein, which interferes with insulin signaling at the IRS-1 level, and the expression of which is increased by TNF-α. It needs to be noted that both insulin resistance and the metabolic changes in lipids that are characteristic of the inflammatory response are also proatherogenic and will hence increase cardiovascular (CV) risk.[1]

What has Incretin/GLP-1 Therapy got to do with Inflammation?

Inhibiting the process of inflammation by various means has consistently been shown to improve insulin resistance and the lipid abnormalities.[1] There is now a reasonable data to suggest that incretin-based therapeutic agents have an anti-inflammatory effect besides their ability to regulate blood glucose, which may provide additional benefits in the treatment of T2DM and perhaps in type 1 DM as well. This effect seems to be a direct one, i.e. independent of the blood glucose lowering effect of incretin/GLP-1 or the effect on weight loss. The most relevant implication of the anti-inflammatory effects of incretin-based therapy is related to atherosclerosis and CV risk.

A basic concept that needs mention here is the difference in anti-inflammatory and immunomodulating actions of GLP-1 agonists (exendin-4-based agents) and the DPP-4 inhibitors (sitagliptin, vildaglptin, and others). The effects on inflammation of GLP-1 agonists are related to their activation of the GLP-1 receptor, which is widely distributed in tissues, including immune cell subpopulations.[2,3] In the case of DPP-4 inhibitors, however, the effects on inflammation are also likely related to the inhibition of CD26, which is responsible for mediating the co-stimulatory second signal of an immune response,[4] rather than solely through GLP-1 receptor.[5] In addition, several other proteins are also substrates for DPP-4, changes in the levels of which may have variable effects. One example of such DPP-4 substrate, which is cardio-active, is the stromal cell-derived factor 1-α (SDF-1α), a chemokine that causes migration of stem cells in humans and rodents and promotes healing of injured endothelium and myocardium, and the activity of which is expected to be enhanced by inhibiting its cleavage by DPP-4.[6]

What is the Evidence Relating Incretin-Based Therapy to Benefits in Inflammation?

Amelioration in the inflammatory processes can be judged by improvement in levels of markers such as plasma C-reactive protein (CRP) and IL-10 or changes in generation of ROS and in tissue expressions of pro-inflammatory factors such as NFkB, JNK, and SOCS-3. The clinical benefits likely to be obtained from these changes should reflect in improvement in end effects of chronic inflammation.

Several studies in animal models have indeed demonstrated benefits with both GLP-1 agonists and DPP-4 inhibitors in endothelial function,[7] atherosclerosis,[8] and hepatic steatosis.[9] Favorable anti-inflammatory effects by way of the action of GLP-1 on adipocytes have also been demonstrated. These effects include an increase in adiponectin secretion from the adipocytes and a switch in the macrophage phenotype in adipose tissue from pro- to anti-inflammatory (switch from M1 to M2). Macrophage infiltration in white adipose tissue also decreases with GLP-1 agonist.[10]

The benefits of the anti-inflammatory effects of GLP-1 have been extended to neuroinflammtory diseases like ischemic stroke and Parkinson's.[11]

Psoriasis is another inflammatory illness, in which clinical improvements have been reported in three patients treated with GLP-1 agonist, the likely mechanism being down regulation of natural killer T-cells.[12]

Two recent studies by Dandona and coworkers[5,13] have separately demonstrated significant anti-inflammatory effects of a GLP-1 agonist exenatide and a DPP-4 inhibitor sitagliptin, each given for 12 weeks in patients with T2DM, by measuring ROS generation and expression of JNK, SOCS-3, IL-1b, TNF-1α, TLR-2, TLR-4, and NFkB DNA binding. Of note was the rapid effect on these markers seen only 2 hours after injecting 5 mg of exenatide. With sitagliptin also, there was a rapid effect, and intranuclear NFkB binding fell significantly at 2 h after a single dose of sitagliptin and lasted for 6 h. The same authors have previously shown a reduction in plasma CRP concentrations and systolic blood pressure, effects that were reversed after cessation of exenatide treatment.

What is the Clinical Relevance of the Effects of Incretin-Based Therapy on Inflammation?

Since vascular complications are now recognized to be an inflammatory disease, the most direct beneficial effects likely to be expected from the ant-inflammatory effects of incretin-based agents are those related to atherosclerosis and CV outcomes. As of date, there are major, multicenter trials ongoing to evaluate CV outcomes with GLP-1 agonists and DPP-4 inhibitors. The preliminary results have revealed minor benefits so far, and have at least not revealed adverse effects on cardiac functions unlike other oral anti-diabetic agents.[6]

Another intriguing application of the anti-inflammatory/immune-modulating effects of incretin-based agents is in salvaging the intact islet cells in type-1 diabetes as shown in the NOD mouse models. Sitagliptin has also been tested in the NOD mouse model and has shown improved islet graft survival. Whether these effects can be extended to salvage b-cell mass in humans is a moot question. Perhaps the ideal candidates would be patients with T1DM of recent onset or in the pre-clinical stages, as a pilot trial of exenatide and CD25 monoclonal antibodies failed to show any effect on residual b-cell function in patients with longstanding T1DM.[14]

Finally, although the future of incretin-based therapy in regulating inflammation in diabetes and its vascular complications seems to be promising, two caveats need to be pointed out. The first is the increase in all cause infections observed with DPP-4 inhibitors, and the second is the controversial risk of chronic pancreatitis with exenatide as well as DPP-4 inhibitors, both underscoring the risks linked to immu.ne suppression caused by these agents. Although clinical evidence for chronic pancreatitis is equivocal, histological evidence of chronic pancreatitis has been shown in rats injected with exendin-4, though the dose used was much higher than that used in humans.[15]

A wiser option, therefore, when riding through a yet unchartered terrain to explore the anti-inflammatory benefits of incretin-based therapy, would be to drive cautiously and keep looking in the rear view mirror for any casualties that we may have left behind.

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