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Lisofylline: a potential lead for the treatment of diabetes

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Abstract

Lisofylline (LSF), a synthetic modified methylxanthine, was originally designed and tested as an agent to reduce mortality during serious infections associated with cancer chemotherapy. Experimental studies and several clinical trials showed that LSF inhibited the generation of phosphatidic acid and free fatty acids. LSF also blocked the release of pro-inflammatory cytokines in oxidative tissue injury, in response to cancer chemotherapy and in experimental sepsis. Recent research has revealed a new potential to extend the therapeutic application of LSF especially for diabetes mellitus. These new studies demonstrate multiple actions of LSF in the regulation of immune cell function and autoimmune response by inhibition of IL-12 signalling and cytokine production. Supporting the new potential for LSF is the discovery of beneficial effects in protecting pancreatic β cells and in preventing autoimmunity. In this article, these new observations about LSF are reviewed and a strategy proposed for using this compound in new clinical applications. LSF may, thus, have therapeutic value in the prevention of autoimmune disorders, including Type 1 diabetes, and autoimmune recurrence following islet transplantation, and in preservation of β cell functional mass during islet isolation.

Keywords: Anti-inflammation; Cytokine; Autoimmunity; Type 1 diabetes; Pancreatic β cell; Islet transplantation

LSF, l-(5-R-hydroxyhexyl)-3,7-dimethylaxanthine (Fig. 1), is a modified methylxanthine with anti-inflammatory properties. Only the ''R'' stereoisomer is biologically active [1], and LSF is inactive in humans after oral administration due to the rapid first pass metabolism [2,3]. In humans, the plasma clearance $t_{1/2}$ values of LSF and its principal metabolites range from 0.75 to 1.17 h after intravenous infusions at doses of 1–3 mg/kg [2].

LSF inhibits stress-activated lipid metabolism, suppresses the production of inflammatory cytokines, reduces toxicity and improves patient responses to cancer chemotherapy and radiation therapy. Although, LSF has been tested in several clinical trials, it still remains in the developmental and experimental stages due to limitations in its therapeutic efficacy. However, recent developments have revealed the potential use of LSF and its analogs in other clinical applications. In this article, we emphasize recent developments in LSF research targeting early prevention of Type 1 diabetes and preservation of isolated pancreatic islet function. We also propose the potential of LSF for these new clinical applications.

LSF has been considered a novel anti-inflammatory compound. As an inhibitor of phosphatidic acid (PA) generation, LSF suppresses the cellular membrane-associated enzyme lysophosphatidate acyltransferase (LPAAT) [4]. Reduction of PA formation and LPAAT activity could suppress host response to TNF-α and IL-1β in inflammatory reaction [5]. For example, LSF, in amount of 100 μM, totally reversed the decrease in insulin secretion caused by IL-lβ-induced PA subspecies (PA-lα) in cultured rat islets [6]. LSF also causes a rapid and prolonged suppression of serum levels of free fatty acids (FFA) in humans. A reduction of total FFA and unsaturated FFA in serum lipid profile might be relevant to the anti-inflammatory activity of LSF, and might serve as a surrogate pharmacodynamic marker of the compound [2], since total FFA and unsaturated FFA are increased in patients with insulin resistance [7,8], rheumatic diseases [9], trauma and sepsis [10].

LSF ameliorates hyperoxia-induced lung injury through inhibiting cAMP response element binding protein (CREB) activation, membrane oxidation and pro-inflam-

Abbreviations: FFA, free fatty acids; LSF, lisofylline; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NOD mouse, non-obese diabetic mouse; PA, phosphatidic acid; scid, severe combined immune deficiency; STAT, signal transducers and activators of transcription; STZ, streptozotocin

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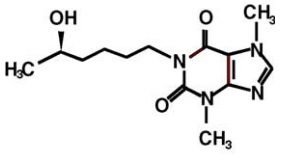

Lisofylline

Fig. 1. Chemical structure of lisofylline.

matory cytokine expression [11]. LSF is effective in treatment for experimental sepsis-induced acute lung injury [12], infectious sepsis [13,14], endotoxic shock [4] and hemorrhagic shock [15]. The effect of LSF in tissue preservation and anti-inflammation depends on its inhibitory action in PA generation, CREB activation, membrane oxidation, pro-inflammatory cytokine production and leukocyte adhesiveness. LSF treatment can ameliorate injury-induced derangement in intestinal structure and function, and improve liver and intestinal mucosal barrier function caused by ischemia and reperfusion [16,17]. The mechanism of such protective effect is due to LSF's ability to preserve micro-vascular perfusion and adenosine triphosphate (ATP) levels. LSF shows similar effectiveness to prevent inflammatory cytokine-mediated β cell dysfunction and cell death by promoting mitochondrial metabolism and enhancing ATP production [18].

LSF was originally designed and previously tested in cancer related therapy. LSF inhibits TGF-β release and facilitates hematopoietic recovery in 5-fluorouracil chemotherapy in mouse models [19], sensitizes p53 mutant human ovarian carcinoma cells to treatment of *cis*-diamminedichloroplatinum [20], and suppresses hematopoietic inhibitors induced by chemotherapeutic agents [21]. LSF was effective in reducing tumor cell survival and suppressing tumor cell growth in a murine mammary carcinoma model [22]. In human studies, LSF inhibits stress-activated lipid metabolic pathways and suppresses circulating levels of the oxidation products of linoleic acid, hydroperoxyl and hydroxyocatadecadienoic acids.

In addition to cancer treatment, LSF was beneficial in transplantation. In a randomized placebo-controlled trial of HLA-identical, sibling-donor, allogeneic bone marrow transplantation, LSF treatment led to a significant improvement in 100-day survival of the grafts [23].

LSF inhibits the gene expression and production of TNF-α, IL-1β, -6, macrophage inflammatory protein (MIP)-lα, TGF-β and IFN-γ, supporting its roles in immunologic regulation [24–26]. LSF blocks IL-12 biological action, reduces IFN-γ production and regulates T cell differentiation and activation [26–29]. IL-12 is also involved in the development of Thl cell-mediated autoimmune disorders, such as multiple sclerosis [26], Type 1 diabetes [30] and autoimmune colitis [31]. Therefore, LSF could be clinically useful for immune regulation and prophylactic therapy for Thl-mediated autoimmune disorders. The ability to inhibit IL-12 signalling through the signal transducers and activators of transcription (STAT)-4 activation has been recognized in mouse allergic encephalomyelitis (EAE), an experimental model of multiple sclerosis [26,32,33]. The reduction of EAE severity by LSF therapy was correlated with the inhibition of Thl cell differentiation and INF-γ production. This effect was associated with blockade of IL-12 mediated repression of the transcription factor GATA-3 and IL-12 induced STAT4 tyrosine phosphorylation [26]. Similar effects were also observed in human T cells [33].

Type 1 diabetes is an autoimmune disorder, characterized by destruction of insulin-producing β cells in pancreatic islets by immune cells, eventually leading to irreversible deficiency of insulin production. The lack of insulin results in disrupted glucose homeostasis and the risk of severe micro- and macro-vascular complications. IL-12 regulates T cell differentiation and Thl cell activation [27]. Since activated T cells directly cause cytotoxicity in β cells, IL-12 may directly and indirectly facilitate the development of Type 1 diabetes [30]. The phosphorylated form of STAT4 is an important signal transducer of IL-12 action. Interruption of the *Stat4* gene results in suppression of T cell activation and reduction of T cell-driven cytokine production [28,29]. LSF, in the amount of 40–100 μM in vitro or 40–60 mg/kg per day intraperitoneally in mice, inhibits STAT4 phosphorylation and reduces inflammatory cytokine production [32–34]. Suppression of T cell activation and reduction of inflammatory cytokine production may protect transplanted tissues (including islets) and reduce the risk of T cell-mediated autoimmune disorders such as Type 1 diabetes.

The nonobese diabetic (NOD) mouse is an established model for human Type 1 diabetes and autoimmune research [35,36]. We have used NOD mice to test the efficacy of LSF in protecting β cells from autoimmunity. LSF (50 mg/kg per day intraperitoneally) effectively prevented autoimmune diabetes development in female prediabetic NOD mice [37]. LSF reduced serum levels of IFN-γ, and diminished cellular infiltration (insulitis) and macrophage presentation in pancreatic islets. LSF also suppressed IFN-γ production in NOD splenocytes in vitro [37].

LSF-mediated anti-diabetic effects are predominantly T cell-mediated, as supported by the observation in adoptive transfer experiments [37]. Adoptive transfer of cells is commonly used for testing cellular effects in an animal model. Adoptive transfer of splenocytes or isolated T cells from overtly diabetic NOD donors induces diabetes in immune deficient NOD.scid mice or accelerates the disease development in young NOD recipients [38]. Prediabetic NOD mice were treated with daily intraperitoneal injection of LSF (50 mg/kg of body weight) for three weeks. Then, splenocytes were isolated for adoptive transfer. NOD.scid mouse recipients failed to develop diabetes after cell transfer. In contrast, splenocytes obtained from saline-treated donors induced diabetes in 95% of recipients

within eight weeks. However, after receiving splenocytes mixed with LSF-treated and saline-treated NOD donors (1:1 by cell numbers), all recipient mice became diabetic. This suggests that LSF may primarily regulate cellular function in treated donors, but does not generate regulatory cells, since no change in the $CD4^+CD25^+$ cell population was found (Yang et al., unpublished data). LSF profoundly reduced macrophage presentation at the site of islets in NOD mice [37]. This finding suggests that LSF may affect the function of macrophages, as well as chemokines and their receptors. A recent study showed that IFN-γ could stimulate the expression of a novel secretoglobin (SCGB) that regulates chemotactic cell migration and invasion [39]. Since LSF reduces IFN-γ mRNA expression and protein production, it is possible that LSF may indirectly reduce the expression and function of SCGB, causing inhibition of chemotactic migration and suppression of cellular invasion to islets.

LSF also protects mice from multiple low-dose streptozotocin (STZ)-induced diabetes [40], another experimental model for studying Type 1 diabetes [41,42]. Experiments indicate that diabetes caused by multiple low doses of STZ is T cell dependent [43] and IFN-γ-related [44]. In the LSF-treated mice, islet infiltration and apoptosis were both markedly reduced, and serum levels of IFN-γ and TNF-α were significantly decreased [40].

An important molecular mechanism explaining the protective effects of LSF has recently been clarified. LSF treatment (40–100 μM) reduces STAT4 phosphorylation in NOD splenocytes by five- to six-fold when compared to the cells from untreated mice. In order to examine the role of STAT4 in autoimmune diabetes development, we have established a new mouse model by cross breeding STAT4 deficient ($STAT4^{-/-}$) mice with NOD mice [45]. In this model, 100 percent of homozygous $STAT4^{-/-}$NOD mice remained diabetes free, while heterozygous $STAT4^{-/+}$NOD showed a delay of disease onset and reduced incidence of diabetes, as compared to gender and age-matched NOD mice. STAT4 mRNA and STAT4 protein were absent, and there was no detectable phosphorylated STAT4 in splenocytes after IL-12 stimulation in $STAT4^{-/-}$NOD mice. These mice demonstrated profound reductions in serum levels of IL-2 and IFN-γ, but similar levels of IL-4, -10 and -12 compared to parental NOD and $STAT4^{-/-}$ mice. The pancreata of $STAT4^{-/-}$NOD mice showed marked reduction of cellular infiltration including the absence of $CD4^+$ and $CD8^+$ T cells in islets and in their vicinity. These results are consistent with the hypothesis that STAT4 deficiency and IFN-γ inhibition reduce cell migration into the islet [45]. These studies provide clear evidence showing a role of STAT4 in autoimmune diabetes pathogenesis and indicate that STAT4 is likely a major target of LSF for anti-diabetic effects.

LSF also has direct protective effects in murine β cell lines and isolated mouse and human islets. LSF, in the amount of 20–100 μM, enhances insulin secretion, improves glucose responsiveness, and increases β cell resistance to apoptosis caused by inflammatory cytokines in a dose-dependent manner [18,37,40,46]. LSF promotes β cell mitochondrial metabolism as reflected by an increase in 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) metabolism and intracellular ATP production. LSF can normalize mitochondrial membrane potential and reduce β cell apoptosis in inflammatory cytokine culture [18]. The mitochondrion controls cell apoptosis [47] and regulates β cell insulin secretion [48]. Therefore, LSF protects β cells by enhancing mitochondrial metabolism.

Autoimmunity recurrence is a major cause for the loss of β cell function after islet transplantation in patients with Type 1 diabetes [49]. The mechanism for the development of autoimmune recurrence is complex, but seems different than that of allogeneic rejection [50]. The destruction of transplanted tissues by autoimmunity is not only limited to islet transplant recipients. Autoimmunity is also observed in transplantation of other organs [51,52], and in patients with other autoimmune disorders [53]. Therefore, control of autoimmunity is an important goal to maintain normal function and viability of the islet grafts in patients with Type 1 diabetes.

General immunosuppression can temporarily control autoimmunity [54] and protect grafted β cells [55]. However, diabetes recurs in islet recipients after either reduction of immunosuppressive medication dosage or change in therapeutic regimen, even when other transplanted organs (such as kidneys) survive [56,57]. These reports suggest that certain types of immunosuppression regimens do not fully control the recurrence of autoimmunity in transplantation. In addition, several immunosuppressive drugs may actually cause autoimmunity [58]. It has been difficult to find an ideal immunosuppressive regimen in β cell replacement for Type 1 diabetes patients. Recently, experimental evidence indicates that LSF significantly reduces autoimmunity in islet transplantation [59]. In the absence of immunosuppression, syngenic islets are destroyed by autoimmune mechanisms in NOD recipients. LSF (50 mg/kg per day, intraperitoneally) protected grafted β cells from autoimmune cytotoxicity after islet transplantation in NOD mice [59]. These new data suggest that LSF may be an effective agent to improve islet function and to control autoimmunity in human islet transplantation.

LSF or its related compounds may have additional therapeutic benefits in preventing the complications of diabetes. LSF protects human kidney mesangial cells from hyperglycemia- and angiotensin II-mediated extracellular matrix deposition [60]. Extracellular matrix accumulation and activation of the renal rennin–angiotensin system are seen in diabetic nephropathy [61,62]. LSF reduced extracellular matrix deposition and TGF-β production in human mesangial cells cultured in high glucose condition. LSF also blocked angiotensin II-induced matrix protein gene expression, including collagen Type IV α-1 and laminin β-1. The

mechanism of LSF's protection in this model was associated with its ability to inhibit the expression of connective tissue growth factor and to suppress the phosphorylation of CREB and p38 MAPK [60,61,63].

In clinical trials, LSF has been given by intravenous bolus infusion (1–3 mg/kg) to healthy volunteers and patients with various conditions, such as: cancer, acute respiratory distress syndrome, or after bone marrow transplantation. These trials demonstrated the safety profile of LSF despite lack of efficacy for these non-diabetic indications.

These new findings provide the rationale for proposing further clinical development of LSF for β cell protection in islet transplantation. LSF is likely effective to supplement the processing solution and culture medium in islet isolation and transplantation [46]. Since LSF promotes mitochondrial metabolism and ATP production, and improves micro-vascular circulation and tissue perfusion, it may protect and enhance β function in early stages of isolation and engraftment. The ability of LSF to suppress pro-inflammatory cytokine production should also protect β cells from cytokine-mediated cytotoxicity. Then, it is possible to use LSF instead of some toxic immunosuppressive medications in islet recipients.

LSF or its analogs could be effective for Type 1 diabetes prevention in high-risk populations, or in patients who are newly diagnosed but with residual β cell function. However, as the requirement for intravenous administration will limit clinical use, orally active LSF analogs are required for their new applications.

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