Life Sciences 231 (2019) 116538

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Effects of novel antidiabetes agents on apoptotic processes in diabetes and malignancy: Implications for lowering tissue damage

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ARTICLE INFO

Keywords:
SGLT2 inhibitor
GLP-1 receptor agonist
DPP-4 inhibitor
Oxidative stress
Apoptosis
Diabetes mellitus
Caspase
Cancer

ABSTRACT

Apoptosis is a complicated process that involves activation of a series of intracellular signaling. Tissue injuries from diabetes mellitus mostly occur as a consequence of higher rate of apoptosis process due to activation of a series of molecular mechanisms. Several classes of anti-hyperglycaemic agents have been developed which could potentially modulate the apoptotic process resulting in fewer tissue damages. Novel types of anti-hyperglycaemic medications such as sodium glucose cotransporters-2 inhibitors, glucagon like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors have shown to provide potent anti-hyperglycaemic effects, but their influences on diabetes-induced apoptotic injuries is largely unknown. Therefore, in the current study, we reviewed the published data about the possible effects of these anti-hyperglycaemic agents on apoptosis in diabetic milieu as well as in cancer cells.

1. Introduction

The global prevalence of diabetes mellitus (DM) is increasing exponentially [1]. Diabetes is responsible for multitude cases of hospitalization, disability and death worldwide [2]. There is a growing evidence that DM induces several pathophysiologic molecular pathways such as oxidative stress, inflammation, fibrosis and apoptosis in various tissues triggering irreversible tissue damage [3–5]. Different classes of anti-hyperglycaemic medications have been developed to normalize blood glucose and prevent of diabetes-related complications [6,7]. If these anti-hyperglycaemic agents could modulate underlying molecular mechanisms of diabetic complications, there is a potential to develop novel potent therapeutic approaches against hyperglycemia-induced tissue injuries [8,9]. Since apoptotic processes have major roles in various types of diabetes dependent tissue damages, in the current study we shed light on possible anti-apoptotic properties of novel antidiabetic medications such as sodium glucose cotransporters-2 inhibitors (SGLT2i), glucagon like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase 4 inhibitors (DPP-4i) in the diabetic milieu and potentially in cancer.

2. Apoptosis

Apoptosis is a distinct feature of programmed cell death which physiologically occurs during many biologic processes such as cell growth, cell differentiation, cell migration, embryonic development, cell turn over, atrophy and cell death [10,11]. In this phenomena, several forms of destruction such as cell shrinking, plasma blebbing, chromatin condensation, nuclear fragmentation, DNA fragmentation and mRNA decay occurs resulting in cell death [10,12]. It has well established that apoptosis is a highly regulated process and is influenced by various stimuli such as free radicals, nutrient deprivation, hypoxia, heat, glucocorticoids, inflammatory mediators, toxins, hyperglycemia, abnormal concentration of ions, invader pathogens, ER (endoplasmic reticulum) stress, radiation, higher concentration of free fatty acids and stress [12,13].

In addition, various biologic agents such as Fas receptors (apoptosis antigen-1), t-Bid (a membrane-targeted death ligand), TLRs (toll like receptors), death receptors, Bax/Bcl2 ratio, TRAIL (tumor necrosis factor related apoptosis inducing ligand) receptors, and p53 protein have potent regulatory effects on onset and progression of apoptotic pathways [12–14] suggesting apoptosis is a very complicated but highly

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https://doi.org/10.1016/j.lfs.2019.06.013
Received 7 May 2019; Received in revised form 3 June 2019; Accepted 5 June 2019
Available online 06 June 2019

regulated energy-consuming cascade of molecular events [10,12]. Both apoptosis progression and inhibition are important since in some condition such as cancer, apoptosis progression helps to prevent metastasis, but in some other milieu such as diabetes kidney disease, we want to suppress apoptosis to lower tissue injuries [12,15].

Apoptosis process is commonly triggered via at least two different molecular pathways viz. intrinsic and extrinsic pathways [12]. While intrinsic pathway is mostly initiated by mitochondria, extrinsic pathway is activated by binding of a apoptotic stimuli to specific plasma membrane receptors leading to complicated intracellular signalings [10,12]. Also, another distinct novel pathway of apoptosis activation has been identified as perforin/granzyme pathway which is activated by binding cytotoxic T lymphocyte cells to specific cellular transmembrane receptors namely perforin and by activating granzyme A or granzyme B which are serine proteases [10,16,17]. In addition, it promotes the activation of different agents such as caspase, proteases and a series of adaptor proteins [10,17].

3. Apoptosis process and diabetes-induced tissue injuries

In addition to the cellular growth and developmental process, apoptosis also has major roles in many forms of tissue injuries as well as in diabetes complications [18,19]. Distinct forms of diabetes-induced cellular damages such as pancreatic beta cell dysfunction, renal glomerular sclerosis, endothelial cell dysfunction, peripheral neuropathy, diabetes dependent memory deficit and vascular incompliance are strongly related to higher levels of un-controlled pathogenic apoptosis which is stimulated by chronic hyperglycemia in patients with diabetes [20–23]. Therefore, diabetes-induced apoptosis a has major role in the pathophysiology of many features of diabetes complications such as diabetic nephropathy, diabetic retinopathy, diabetic neuropathy and cardiovascular disorders [19,24].

Higher concentrations of circulatory glucose can be a potent inducer for apoptosis by activating the aforementioned proapoptotic agents and dysregulation of normal physiologic cell cycle toward death (Fig. 1) [14,19,24]. Also, diabetes indirectly increases apoptosis-related cellular damages by potentiating other stimuli of apoptosis such as oxidative stress and inflammation [24]. Consequently, apoptotic process results in higher rate of tissue dysfunction in patients with diabetes with respect to diabetes complications such as diabetic kidney disease [14,19].

4. Novel antidiabetic agents of SGLT2i, GLP-1RA and DPP-4i at a glance

SGLT2 inhibitors (SGLT2i) are a newly diagnosed family of antidiabetic medications which decrease circulatory glucose by inhibition of renal tubular glucose reabsorption and induction of urinary glucose excretion [25,26]. These antihyperglycaemic agents act completely independent of insulin secretion and are only correlated to circulating glucose. They also do not have the risk of hypoglycaemia [27]. After the discovery of was the first SGLT2i phlorizin, other agents in this class have been developed which reduce blood glucose nearer to the level of the glucose reabsorption capacity of nephrons [27–30]. They also have other anti-hyperglycaemic actions such as inhibition of gluconeogenesis, improvement of insulin sensitivity, increasing the glucagon response and stimulating insulin secretion from the beta cells of pancreas [31–34].

GLP-1 RA is another class of recently introduced anti-hyperglycaemic agents that was first approved by FDA in 2010 for the management of diabetes [8]. They act as a potent agonist for GLP-1 receptors and thereby mimic the effects of incretin hormones. They are a family of metabolic hormones secreted by the gastro-intestinal tract that reduce postprandial circulatory glucose via inhibition of glucagon secretion from pancreatic α-cells and stimulating insulin release from β-cell in a blood glucose dependent manner [35–38]. They can also provide additional anti-hyperglycaemic effects by delaying the gastric emptying, appetite suppression, reduction in nutrient absorption and improvement of lipid metabolism [38–40]. These drugs act by biding to GLP-1R that are predominantly expressed in islets' β-cells [35].

DPP-4 inhibitors (DPP-4i) are the other novel class of antidiabetes agents which produces antihyperglycemic effect by inhibiting GLP-1 inactivation and thereby raising the active levels of GLP-1 [41,42]. After post-translational processes of pre-glucagon (PG) peptides in the intestinal cells, at least four distinct forms of PG released which are all inactivated by DPP-4 enzyme via removing the two amino acids from their N-terminal residue [43]. As a result, the DPP-4i have similar but less potent antihyperglycemic effects to GLP-1 agonists, although they may show some differences on weight loss and the risk of adverse effects [42].

5. SGLT2i and apoptosis

In recent years, some studies have focused on the possible effects of SGLT2 inhibition on apoptosis process [44,45]. Their findings strongly suggested that these agents could influence apoptosis by inducing as well as suppressing apoptosis in differing conditions (Tables 1 and 2) [45,75]. While empagliflozin therapy can inhibit beta cell apoptosis in pancreatic cells, ipragliflozin induces apoptosis in MCF-7 cells (human breast cancer cell line) [46,64]. These findings suggest that SGLT2 inhibition results in progression or inhibition of apoptosis in different disease states [46,64]. In fact, either progression or inhibition of apoptosis are potential therapeutic targets in distinct conditions such as diabetes complications or cancer [12].

5.1. SGLT2i and apoptosis inhibition

Cheng et al. in 2016 demonstrated that empagliflozin inhibited beta cells apoptosis via ameliorating glucotoxicity-induced oxidative stress

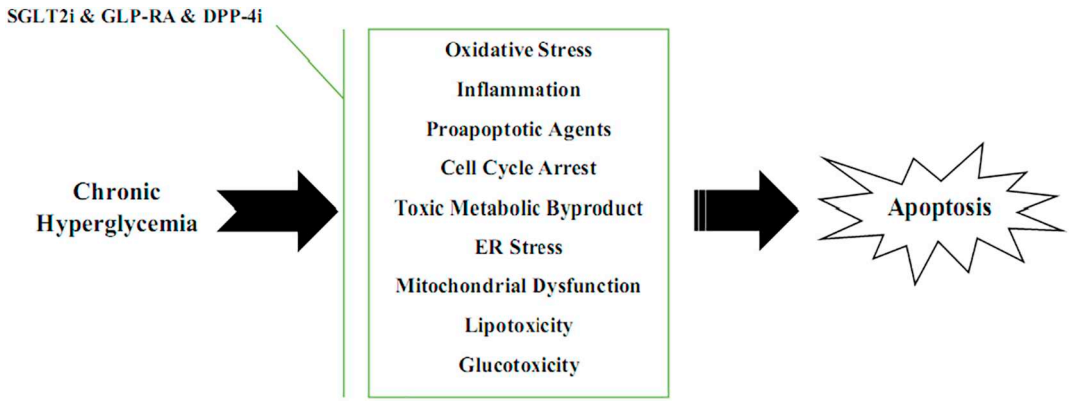

Fig. 1. Main molecular mechanisms between diabetes mellitus and apoptosis and the possible modulatory roles of SGLT2i, GLP-RA and DPP-4i.

Table 1
Main evidences about apoptosis inhibition by novel antidiabetic drugs.

		Inhibitory effects on apoptosis	Ref.
SGLT2 inhibitors	Dapagliflozin	Prevented of obesity-induced apoptosis by attenuation of oxidative stress, ER stress and obesity	[44]
	Empagliflozin	Inhibited beta cell apoptosis via ameliorating glucotoxicity	[46]
	Dapagliflozin	Provide neuroprotective effects by preventing oxidative stress induced apoptosis in brain	[45]
	Dapagliflozin	Reduces apoptotic processes in renal diabetic tissue	[47]
	Empagliflozin	Protected renal proximal tubular cells from apoptosis by correcting lipid metabolism and reducing intra-renal lipotoxicity	[48]
	Dapagliflozin	Inhibited apoptosis by attenuating inflammatory responses and oxidative stress	[49]
	Dapagliflozin	Reduced oxidative stress dependent apoptosis in diabetic kidneys of mice	[50]
	Luseogliflozin	Preserved pancreatic beta cell mass by suppressing apoptosis in diabetic mice	[51]
	Tofogliflozin	Prevented of oxidative stress dependent apoptosis in renal proximal tubules of human cultured proximal tubular cells	[52]
	siRNAs against SGLT2	Prevented of AGEs-induced apoptosis in proximal tubular cells exposed to high glucose concentrations	[53]
	Dapagliflozin	Slows the progression of kidney tissue injuries by suppressing apoptosis via attenuating oxidative stress and inflammation in diabetic animals	[54]
GLP-1RA & DPP-4i	GLP-1 peptide	Inhibit beta cells' apoptosis by caspase-3 down-regulation and the up-regulation of bcl-2	[55]
	Vildagliptin	Attenuated neuronal apoptosis by improving mitochondrial function and ameliorating inflammation	[45]
	Exenatide	Reduces β-cells' apoptosis and induces islets' neogenesis by attenuating inflammatory cytokines as IL-1β, TNF-α, and IF-γ in diabetic rats	[56]
	Exenatide	Makes beneficial effects on β-cell survival and function by increasing Akt signaling pathway, SIRT1 and α-Klotho up-regulation leading to apoptosis suppression in human cultured islet cells	[57]
	GLP-1 peptide	Protect against apoptosis by improvement in mitochondrial function and PKA and PI3K signaling pathways	[58]
	Exenatide	Prevents inflammation-induced apoptosis by a PKB-dependent mechanism	[59]
	GLP-1 peptide	Prevents apoptosis by induction of IGF-1 receptor expression and reducing inflammatory mediators leading to cAMP activation and beta cells' regeneration	[60]
	GLP-1 peptide	Protects cardiomyocytes by suppressing apoptosis through PI3K and ERK1/2 dependent pathways	[61]
	Diprotin A	Inhibits apoptosis in endothelial cells by making cytoprotective effects in human umbilical veins	[62]
	Desfluorositagliptin	Prevents beta cells' apoptosis by down-regulating proapoptotic agents in diabetic mice	[63]

IL-1β = interleukin-1 beta, IF-γ = interferon-gamma, SIRT1 = sirtuin-1, α-Klotho = anti-aging protein, PKB = protein kinase b, IGF-1 = insulin like growth factor-1, PKA = protein kinase a, PI3K = Phosphoinositide 3-kinase, ERK1 = Mitogen-activated protein kinase 3, AGE = advanced glycation end product, ER = endoplasmic reticulum, siRNA = small interfering RNA.

[46]. They suggested that hyperglycemia-dependent oxidative stress has upstream effect on apoptosis and thereby, lowering blood glucose by SGLT2 inhibition, reduces apoptosis and increases beta cell mass in diabetic animals [46]. Nipon et al. in 2018 established that SGLT2 inhibition using dapagliflozin prevent obesity-induced apoptosis by attenuation of oxidative stress, ER stress and obesity in renal tissues of diabetic rats [44].

Sa-nguanmoo et al. in 2017 have shown that dapagliflozin can exert neuroprotective effects by preventing inflammation and oxidative stress in brain tissue leading to amelioration of apoptosis process and improving cognitive function in obesity-induced insulin resistant rats [45]. Another study demonstrates that dapagliflozin attenuated apoptotic processes by reducing renin-angiotensin system (RAS) activity and lowering oxidative stress in renal tissue of diabetic animals [47]. Moreover, Lee and coworkers in 2018 demonstrated that SGLT2 inhibition by empagliflozin protected renal proximal tubular cells from apoptosis by reducing intra-renal lipotoxicity in HK2 cells treated with high glucose concentration [48]. They also found that empagliflozin upregulated the Bcl-2 and downregulated the t-Bid, Bax and cytochrome-C protein expression and inactivated the caspase-3, 8 and 9 in kidney tissues [48]. Moreover, Staels et al. in 2017 suggested the anti-apoptotic potentials of SGLT2i in cardiovascular network as cardioprotective effects of these antidiabetic agents [76]. These data (Table 1) strongly suggest that SGLT2 inhibition ameliorates apoptosis mainly via suppressing oxidative stress in the diabetic milieu [51].

5.2. SGLT2i and apoptosis progression

Some evidences indicated that SGLT2 inhibition can induce apoptosis process in conditions such as cancer [64]. Komatsu and colleagues in 2018 found that ipragliflozin markedly increases apoptotic processes in breast cancer cells [64]. Also, Kuang and coworkers in 2017 demonstrated that dapagliflozin induces apoptotic events and reduces tumor volume in human renal cancer cells [65]. SGLT2 inhibition with canagliflozin induces remarkable apoptosis processes in human hepatocellular carcinoma cells [66]. These evidences imply that SGLT2i therapy in cancer cells promotes apoptosis unlike diabetic milieu in which SGLT2i suppress apoptosis (Table 2) [53,54]. These data strongly suggests that SGLT2i have beneficial effects on apoptotic processes and can induce them in such conditions as cancer, but inhibit them in

Table 2
Main evidences about apoptosis induction by novel antidiabetic agents.

		Stimulatory effects on apoptosis	Ref.
SGLT2 inhibitors	Ipragliflozin	Induces apoptosis in the breast cancer cells via membrane hyperpolarization and mitochondrial dysfunction	[64]
	Dapagliflozin	Increased the early and late cellular apoptosis in human renal cancer cells	[65]
	Canagliflozin	Induces apoptotic processes in human hepatocellular carcinoma cells	[66]
	Phlorizin	Stimulates apoptosis by up-regulating the BCL2, activation of caspase-3, reduces ATP level and mitochondrial membrane potential and arrest cell cycle in human hepatocellular carcinoma HepG2 cells	[67]
GLP-1RA & DPP-4i	Sitagliptin	Increases apoptosis process in human cultured colon cancer cells	[68]
	DPP-4i	DPP-4 up-regulated in cancer cells due to positive effects on apoptosis	[69]
	Exenatide and liraglutide	Induce apoptosis by raising Bax/Bcl-2 ratio and activating p38 molecular mechanisms in human prostate cancer cells	[70]
	GLP-1R expression	Implicated in prostatic cancer progression and modulates it by apoptosis induction	[71]
	Exenatide	Increases apoptosis by cAMP dependent mechanism in murine colon cancer cells	[72]
	Exenatide	Attenuates prostate cancer growth through apoptosis induction via ERK-MAPK pathway inactivation	[73]
	Liraglutide	Attenuates tumor size by apoptosis induction via AMPK signaling pathways	[74]

AMPK = AMP-activated protein kinase, cAMP - cyclic adenosine monophosphate.

pathologic conditions such as diabetic kidney diseases [52,53,66,67].

6. GLP-1RA & DPP-4i and apoptosis

Induction of GLP-1 receptors by related agonists/medications may modulate apoptosis process [45,77] (Table 1). Addition of GLP-1 peptide in human cultured beta cells preserved its mass and inhibited apoptosis by caspase-3 down-regulation and the up-regulation of bcl-2 [55]. Extedinn-4, one of the GLP-1 peptides, reduces beta cells' susceptibility to apoptosis and induces islets' neogenesis by attenuating inflammatory cytokines as IL-1β (interleukin 1β), TNF-α (tumor necrosis factor α), and interferon-γ in diabetic animals [56]. They can also ameliorate beta cell apoptosis and maintain islets mass [77]. GLP-1 addition to human cultured islets inhibited apoptosis by induction of IGF-1 (insulin like growth factor-1) receptor expression and attenuating inflammatory mediators leading to activating specific G-protein dependent receptors; cAMP activation and beta cells' regeneration [60]. Vildagliptin (DPP-4i) therapy in obese rats improves brain function via attenuating neuronal apoptosis, although its effects was weaker compared to dapagliflozin [45].

Reviewed data suggest that GLP-1R activation can suppresses apoptosis and reduces tissue injuries by different mechanisms to SGLT2i. These includes various molecular mechanisms such as IGF-1 activation, caspases inactivation, PKB, PKA, PI3K and SIRT1 signaling pathways and improvement of mitochondrial function in the diabetes milieu [45,55,57–60]. Similar findings have been observed on the effect of DPP-4i effects on apoptosis [62,63]. Evidence indicates that using DPP-4i in diabetic milieu can reduces apoptotic processes by different molecular mechanisms such as down-regulating proapoptotic agents and making cytoprotective effects [62,63].

In contrast, in cancer cells; there is growing evidence that these agents could protect tissues by apoptosis induction and have anti-cancer effects. One of the DPP-4i, sitagliptin, markedly promotes apoptosis process and have anti-cancer effects in human cultured colon cancer cells [68]. DPP-4 expression is also correlated to cancer progression suggesting that DPP-4i may have a modulatory effects on these cells by induction of apoptosis [69]. Exenatide and liraglutide (GLP-1RA) both induce apoptosis by raising Bax/Bcl-2 ratio and activating p38 molecular mechanisms in human prostate cancer cell lines [70] (Table 2). However, some evidences are contrary to these findings [78]. Koehler et al. in 2006 found that treatment by extendin-4 did not modify apoptosis in human pancreatic carcinoma cells and was not effective in lowering tumor size [78]. Exendin-4, another GLP-1RA was also unable to modify tumor size in prostatic cancer cells [79].

7. Conclusion

Beyond physiologic roles, apoptosis has a major involvement in tissue injuries induced by pathologic conditions such as diabetes mellitus and cancer. Many forms of cellular injuries in diabetes related complications are a result of higher rate of uncontrolled apoptosis under influences of a varied stimuli including glucotoxicity, inflammatory cytokines and free radicals. In this milieu, SGLT2i can reduce tissue injuries by lowering glucotoxicity, lipotoxicity, oxidative stress, inflammatory responses and ER stress leading to fewer rate of apoptosis. There is a growing evidence that SGLT2i agents can potentially suppress apoptosis events in diabetic milieu. In contrast, in malignant cells, SGLT2 inhibition induces apoptosis processes; there by potentially reducing tumor size. They can potentially stimulate apoptosis by different molecular mechanisms such as up-regulating the BCL2 and modulating BAX/BCL2 ratio, activation of caspases, reducing intracellular ATP level, induction of mitochondrial dysfunction and exerting arrest in cell cycle in malignant tissues. Our study shows that SGLT2 inhibition has remarkable effects on apoptosis and if modulated toward therapeutic targets; they are likely to induce apoptosis in cancer cells, but inhibit it in diabetic milieu. These findings suggest new therapeutic potential for the management of tissue injuries in either patients with diabetes or with cancer; especially hepatocellular and colon cancers.

Moreover, induction of GLP-1 receptors by anti-hyperglycaemic agents such as GLP-1RA or DPP-4i have potent influences on apoptotic processes. Emerging evidence suggests that GLP-1R induction markedly reduces tissue damages by suppressing apoptotic pathways. This could be potentially mediated through molecular mechanisms such as down-regulating proapoptotic agents such as caspase-3, improving mitochondrial function, ameliorating inflammatory mediators as IL-1β, TNF-α, and IF-γ, attenuating oxidative stress, by several intracellular signalings as Akt, PKA, PI3K, cAMP, and ERK1/2 dependent signaling pathways, bcl-2, SIRT1, α-Klotho and IGF-1 receptor up-regulation, beta cells' regeneration and by making cytoprotective effects in diabetic milieu. Similarly, they might induce apoptotic death in cancer cells. There is emerging evidence to imply that GLP-1R induction induces apoptosis events by different molecular pathways such as raising Bax/Bcl-2 ratio and activating p380induced apoptosis as well as through signaling pathways as ERK-MAPK and MAPK dependent signaling. Conversely, some data suggest that they are unable to modulate apoptotic pathways in carcinoma cells.

In conclusion, based on the reviewed data, both SGLT2 inhibition and GLP-1R activation have inhibitory effects on apoptotic events and reduce tissue injuries in diabetes related complications thereby in addition to their anti-hyperglycaemic effects, they can be considered as anti-apoptotic agents. Also, SGLT2i are more likely to be potent than GLP-RA and DPP-4i for apoptosis induction in cancer cells and can decline tumor size by enhancing cellular death in distinct types of cancers.

Declaration of Competing Interest

The authors clearly declare that have no conflict of interest in this study.

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