Spermidine may decrease ER stress in pancreatic beta cells and may reduce apoptosis via activating AMPK dependent autophagy pathway


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A B S T R A C T
The risk for diabetes increases with increasing BMI < 25. Insulin resistance is the key factor for type 2 diabetes; studies revealed that endoplasmic reticulum stress is the main factor behind this disease. With increase in ER stress, pancreatic beta cells start to undergo apoptosis, leading to a decline in the pancreatic beta cell population. The ER stress arises due to unfolded protein response. Recently, spermidine get importance for increasing the longevity in most of the eukaryotes including yeast, Caenorhabditis elegans, Drosophila and human peripheral blood mononuclear cells via induction of autophagy pathway. Autophagy is also involved in regulation of scavenging of proteins. One of the major cellular pathways for scavenging the aggregated intracellular protein is autophagy. Hence spermidine can be a candidate for the treatment type 2 diabetes. Autophagy genes are regulated by mTOR (mammalian Target Of Rapamycin) dependent or independent pathway via AMPK. Hence either inhibition of mTOR or activation of AMPK by spermidine will play two crucial roles, first being the activation of autophagy and secondly the reduction of endoplasmic reticulum stress which will reduce beta cell death by apoptosis and thus can be a novel therapeutic candidate in the treatment of insulin resistance in type 2 diabetes and preserving pancreatic beta cell mass.

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I ntrodu ction

Diabetes is spreading worldwide as an epidemic. Insulin resistance is a key factor behind type 2 diabetes. The pancreatic beta-cell senses nutrients, neurotransmitters and hormones in the circulating blood. The unique function of the cell is to integrate all these ambient signals into an appropriate insulin secretory rate in order to maintain normal glucose homeostasis [1]. Insulin resistance and decreased insulin production by pancreatic beta-cells are recognized as the primary defects in type 2 diabetes [2]. In many pre-diabetic insulin-resistant individuals, the beta-cells often produce excessive quantities of insulin in order to compensate for insulin resistance. Evidences suggest that endoplasmic reticulum stress is the cause behind insulin resistance state [3,4]. Endoplasmic reticulum (ER) stress occurs when protein folding and modification are disrupted; triggering a complex protective response termed the unfolded protein response (UPR) [5]. The unfolded protein response (UPR) play a dual role in beta-cells, acting as beneficial regulators under physiological conditions or as triggers of beta-cell dysfunction and apoptosis under situations of chronic stress [6]. Novel findings suggest that chronic high glucose and fatty acid exposure, contribute to beta-cell failure in type 2 diabetes. Endoplasmic reticulum (ER) stress is necessary for the promotion of apoptosis in beta cells in both animal models of diabetes and of humans with type 2 diabetes [7]. When unfolded protein accumulates secondary to a mild stress, universal protein synthesis is inhibited, but then resumes upon recovery, but in more severe or persistent stress would lead to apoptosis [8]. Reducing the rate of synthesis of protein will be helpful in restoring the endoplasmic reticulum stress, and scavenging of unfolded proteins through autophagy will be a benefit in recovery of the cell from the stressful condition. The regulation of protein synthesis and autophagy comes under the governance of mTOR. The Eukaryotic Initiation Factor 4 (elf4) groups are the downstream target for mTOR, these factors mediate key steps in translation initiation, such as the recruitment of the mRNA to the small (40S) ribosome subunit and the recruitment of the initiator methionyl-tRNA (Met-trNA) that recognizes the start codon at the beginning of the coding region [9].

Spermidine is a polyamine compound, found in ribosomes and living tissues, originally it was isolated from semen from which
it derived its name. Spermidine is a triamine structure that is produced by spermidine synthase (SpdS) which catalyzes mono-alkylation of putrescine (1,4-diaminobutane) with decarboxylated S-adenosylmethionine (dcAdoMet) 3-aminopropyl donor [10]. The formal alkylation of both amino groups of putrescine with the 3-aminopropyl donor yields the symmetrical tetraamine spermine [11].

Decrease in polyamine level is found to induce pancreatitis [12], polyamine supplementation is found to reduce chemical induced pancreatic inflammation [13] indicating that the polyamine level should be in optimal level, and decrease of this level may lead to disorders. Pancreatic spermidine level in pancreas of diabetic animals were found to be lower comparing to the normal animals [14].

Autophagy is a mechanism in which portions of the cytoplasm are sequestered within autophagosomes and then targeted to lysosomes for digestion. Recent evidence suggests that autophagy usually mediates cytoprotection, thereby avoiding the apoptotic or necrotic demise of stressed cells [15,16].

Spermidine is reported to increase the life span in many model organism including nematodes (Caenorhabditis elegans), yeast (Saccharomyces cerevisiae), and flies (Drosophila melanogaster) and significantly reduces age related oxidative protein damage in mice [17].

A recent study revealed that, administration of spermidine, a natural polyamine whose intracellular concentration declines during human ageing, markedly extended the lifespan of yeast, flies and worms, and human immune cells through induction of autophagy [18]. Study led by Morselli et al. showed that spermidine do not affect the phosphorylation of mTOR and neither effects its substrate ribosomal protein S6 kinase, which reveals that spermidine induces autophagy through AMPK dependent pathway [19].

**AMPK/mTOR in protein synthesis and autophagy regulation**

AMP-activated protein kinase (AMPK) inhibits mTOR in response to reduced ATP levels [20]. AMP activated protein kinase suppress protein synthesis by down regulating the mTOR signaling cascade [21–23]. mTOR regulates numerous components involved in protein synthesis, including initiation and elongation factors, and the biogenesis of ribosomes themselves [24]. Low insulin/IGF-1 signaling, nutrient or energy deprivation, and stress converge to down regulate the activity of the protein kinase target of rapamycin (TOR) [25]. Inhibition of mTOR stops the protein synthesis machinery due to inactivation of its effector, p70 S6 kinase and activation of the eukaryotic initiation factor 4E binding protein 1 (4E-BP1), an inhibitor of translation [26]. Autophagy associated genes are under the regulation of mTOR [27]. Rapamycin which is an inhibitor of TOR, enhances autophagy by inhibition of the TOR [28]. Suppressing mTOR activity induces autophagy, a lysosomal catabolic pathway for turnover of proteins and organelles.

**Activation of autophagy inhibits apoptosis- and vice versa**

There are enough publications as an evidence to support the fact that activation of autophagy reduces or inhibit the apoptosis and vice versa. AMPK is an energy sensor that mediates autophagy and inhibits apoptosis [29]. Whereas; autophagy inhibition increases the chances of apoptosis. The genetic inhibition of autophagy by knockout or knockdown of ATG genes often lead to apoptotic or necrotic death of cells [30–32], chemical inhibition of autophagy through PI3K/Akt using sodium selenite increases NB4 cell apoptosis [33], which clearly reveals that inhibition of autophagy contributes to the up-regulation of apoptosis. Autophagy inhibition enhances anthocyanin-induced apoptosis in hepatocellular carcinoma [34]. Thus, activation of autophagy inhibits apoptosis and inhibition of autophagy activates apoptosis.

**Hypothesis**

Spermidine had shown to induce autophagy in most eukaryotes. Hence spermidine can be used to induce autophagy in pancreatic beta cells (Fig. 1), which can reduce the stress load raised due to unfolded protein response. Autophagy induction is an indirect message that protein synthesis is in suspended state, hence it is possible it could benefit in restoration of endoplasmic reticulum stress raised due to unfolded protein response. This will provide sufficient time for the beta cells to recover and the apoptosis induced beta cell death will be reduced. Hence spermidine can be a potent candidate in preserving beta cell mass which are reduced due to apoptosis induced cell death in type 2 diabetes mellitus.
Conflict of interest

None declared.

References