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Association between Type-2 diabetes and Parkinson’s disease: a cross-talk between amylin and α-synuclein

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Short Communication

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ABSTRACT
Assembly of intrinsically unfolded polypeptide into amyloid fibers plays an important role both in type-2 diabetes and in Parkinson's disease. In type 2 diabetes amylin [islet amyloid polypeptide (IAPP)] may be converted to amyloid structures, whereas in Parkinson’s disease α-synuclein forms amyloid like inclusions implicated in the pathogenic mechanism. The role of two other members of the synuclein family, β- and -synuclein is not investigated in detail. Recent data suggests the existence of cross-talks between IAPP and α-synuclein in amyloidogenesis and the contribution of other factors which make their interaction more complicated. Investigation of molecular mechanisms involved in this network may reveal new targets for the treatment of both diseases.
SHORT COMMUNICATION

The etiology of type-2 diabetes and Parkinson’s disease are very different, however, there is an association between these disorders: the risk of Parkinson’s disease is approximately 40% higher among diabetic patients than among participants without diabetes \[^{1,2}\], advocating a shared mechanism between these diseases. Indeed, these two disorders share several common molecular mechanisms, including protein misfolding, aggregation and amyloid formation \[^{3,4}\]. Type-2 diabetes is a disease involving formation of amyloid which takes place in the pancreas. The process of islet amyloid formation from amylin or islet amyloid polypeptide (IAPP, 37 residues, natively unfolded polypeptide) \[^{5}\] causes pancreatic β-cell dysfunction, cell death, and development of diabetes. Another amyloidogenic protein, α-synuclein (140 amino acids) \[^{6,7}\] is expressed in several organs, including pancreatic islet b-cells where it modulates insulin secretion \[^{8,9}\].

α-Synuclein is a member of the synuclein family consisting of three members, α-, β- and γ-synucleins \[^{6,7}\]. Synucleins are small naturally unfolded or intrinsically unstructured proteins implicated in neurodegenerative and some other human diseases. One of the mechanisms of their involvement in diseases is due to their ability to form amyloid-like fibers. Formation of toxic α-synuclein aggregates and Lewy bodies consisting basically from α-synuclein is a hallmark of Parkinson’s disease. It is widely recognized that metal ions such as copper (II) are implicated in the aggregation process of both α-synuclein and IAPP \[^{10}\].

Recent studies point to the existence of a cross-talk between α-synuclein and IAPP in their amyloidogenic pathways \[^{11}\]. In a recent article published in the Proceedings of the National Academy of Sciences (PNAS U S A) two researchers from Gothenburg (Sweden) Horvath and Wittung-Stafshede described the existence of network of cross-reactivity between these two amyloidogenic proteins, including the acceleration of α-synuclein amyloidogenesis in the presence of IAPP \[^{11}\]. This cross-reactivity may explain why patients with type 2 diabetes are vulnerable to Parkinson’s disease. Interestingly, IAPP in vitro forms amyloids much faster compared to α-synuclein (minutes versus hours).

Monomers of IAPP and α-synuclein easily coaggregate forming heterologous amyloid fibers, while preformed amyloid fiber seeds from a faster/slower aggregating protein accelerate/inhibit aggregation of an intrinsically slower/faster aggregating protein (Figure 1). The authors explain this tendency by an inherent “memory” in the amyloid seed that becomes transmitted into newly formed amyloids and thus dictates the aggregation speed of the other protein \[^{11}\].

In earlier genetic research another important link has been established between type 2 diabetes and Parkinson’s disease. Genome-wide association studies (GWAS) have demonstrated an association between Zn metallopeptidase IDE (insulin-degrading enzyme) and type-2 diabetes \[^{12,13}\]. In other studies, two groups of researchers have found that IDE mutant mice have elevated level of α-synuclein in pancreatic islets \[^{9,14}\]. IDE is a conserved metallopeptidase that can degrade in the pancreas insulin and a variety of other small peptides including IAPP \[^{15,16}\].
Importantly, α-synuclein is localized in insulin-secretory granules in pancreatic beta-cells and presumably is associated with insulin biogenesis and exocytosis \[^8\], whereas IDE binds to C-terminus of α-synuclein oligomers (residues 96–140, Figure 1) forming stable SDS-resistant complex, inhibits its amyloidogenesis and in parallel IDE proteolytic activity toward insulin significantly increases \[^8,17,18\]. C-terminal fragment of α-synuclein consisting of 44 residues enhances IDE proteolytic activity to the same degree as full-length α-synuclein. This interaction takes place due to electrostatic interaction between acidic α-synuclein C-terminus and basic IDE exosite \[^17\]. Since this binding inhibits α-synuclein amyloidogenesis and simultaneously increases the proteolytic activity of IDE, the interaction may be considered as a target for the treatment of both diabetes and Parkinson’s disease.

Another important link between α-synuclein and diabetes is due to its involvement in glucose regulation and negative effect on insulin secretion through K-channel modulation in beta-cells of the pancreas \[^12,16,17\]. α-Synuclein measurements in serum in a large population have shown that low α-synuclein levels are associated with insulin resistance \[^19,20\].

Another common contributing factor in diabetes and Parkinson’s disease is dopamine deficiency. Dopamine is a key player in Parkinson’s disease and its decrease is an important factor in diabetes and its complications, such as diabetic retinopathy. Curiously, some researchers even consider diabetic retinopathy as the Parkinson’s disease of the eye \[^21\]. These new results can explain the mechanism of association between diabetes and Parkinson’s disease described previously \[^22,23,24\].

Several studies demonstrate an association of another member of the synuclein family, γ-synuclein with diabetes. Altered expression of γ-synuclein gene in the hippocampus and prefrontal cortex was reported in type 2 diabetic rat model in comparison to non-diabetic control animals \[^25\]. Reduced γ-synuclein expression was also described in retinal ganglion cells in a rat model of diabetes \[^26\]. To the contrary, in skeletal muscle of high-fat diet-induced obese mice, γ-synuclein expression is significantly elevated \[^27\]. Mechanism of involvement of γ-synuclein in diabetes is still unclear, but may be associated with its role in the regulation of metabolic processes in adipocytes and the maintenance of adipocyte lipid droplets and aberrant lipid metabolism \[^28\]. γ-Synuclein easily changes its intracellular localization and its expression is regulated on both transcriptional and post-transcriptional levels \[^29,30,31,32\]. There is no data about a role of β-synuclein in the pathogenesis of diabetes and Parkinson’s disease, however, since β-synuclein inhibits α-synuclein aggregation \[^33\] there is doubt that its role may be similar to α-synuclein.
**FIGURES with LEGENDS**

[Fig-1]

**Figure 1.** Full-length α-synuclein can be divided into three distinct domains, the N-terminal domain (residues 1–60) which is amphipathic and responsible for binding to phospholipids; the non-amyloid-β component (NAC) domain (residues 61–95) which is highly hydrophobic and essential for aggregation, and the acidic negatively charged C-terminal domain (residues 96–140) critical for the chaperone-like activity and IDE binding. C-terminal fragment 98-140 is involved in IDA binding.

[Fig-2]

**Figure 2.** Scheme explaining the effects on amyloid formation reactions among IAPP, α-synuclein, pro-IAPP monomers and amyloid seeds. The amyloid seeding reactions can be summarized by a statement “faster makes faster and slower makes slower” [11].
REFERENCES


