Ben-Gurion University of the Negev
אוניברסיטת בן-גוריון בנגב

Graduate Students Seminar

Department of Chemistry

Monday, June 26th, 2023
Time 10:00
Bldg. 43 Room 015

Shira Ben-Shushan

Under the supervision of Prof. Yifat Miller

Neuropeptides as Metal Ion Chelators for Inhibiting Insulin Aggregation

Insulin is an amyloid hormone that is naturally released from the β-cells in the pancreas. It plays a central role in controlling the blood sugar level and it is considered the main therapy strategy in patients with type 2 diabetes (T2D). However, during insulin therapy, this hormone forms amyloid fibrils at the repeated site of injection. The pathology of these fibrils causes serious therapeutic problems. Zinc ions share the same secretory path with insulin, and even play a key role in the synthesis and action of insulin. It is known that insulin aggregation undergoes in presence and in absence of zinc ions. Neuropeptides (NPs) are neuronal signaling molecules that are produced and distributed in the central nervous system. It is hypothesized that these NPs have the ability to bind metal ions, e.g. Zn2+, and serve as metal chelators for amyloid aggregation. Therefore, this study suggests NPs to serve as metal chelators to inhibit insulin aggregation. Neurokinin A (NKA), neurokinin B (NKB), substance P (SP)1 and neuropeptide Y (NPY)2, which are the most abundant NPs, were examined.
Molecular Dynamics (MD) simulations were applied to investigate the effect of NPs as metal ion chelators to inhibit insulin aggregation.

To this aim, (1) possible binding sites for Zn2+ were tested in the NPs. (2) Various Zn2+ binding sites were determined within insulin fibrils,3 and, (3) the NPs were bound to Zn2+-insulin fibril-like oligomers to examine the competition between NPs and insulin on the Zn2+ ions, and to study the inhibition of insulin aggregation. Our results demonstrate that NPY successfully competes with insulin fibril-like oligomers on the Zn2+ binding sites. In addition, NPY disrupted β-strands in the seeding domain of insulin. Therefore, among all the NPs that were examined, NPY serves as a good metal chelator agent and the best NP for inhibiting insulin aggregation.

References

1. S. Ben-Shushan, et. al. Inorg. Chem. (2020), 59, 925-929.
2. S. Ben-Shushan, Y. Miller. Inorg. Chem. (2021), 60, 484-493.
3. S. Ben-Shushan, Y. Miller. Inorg. Chem. Front. (2021), 8, 5251-5259.