COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
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25th John G. Wagner Lecture

Wednesday, September 23, 2020
https://umich-health.zoom.us/j/5652976039
12:00-1:00pm

"Phosphate esters of glucagon for hypoglycemia"

Presented by:

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Abstract: Glucagon is a 29-amino acid peptide hormone used in the emergency treatment of severe hypoglycemia. Glucagon is poorly soluble in aqueous solution at neutral pH and is administered in acidic solutions. However, glucagon is not stable even in acidic solution, in which it rapidly and irreversibly forms insoluble amyloid β-fibrils. Glucagon amyloid fibril formation compromises the potency of the drug, has the potential to generate toxic effects, and increases solution viscosity which causes difficulty in delivering the formulation using an infusion pump or injection pen. Due to these solubility and stability issues, glucagon is currently formulated as a lyophilized powder that is reconstituted just prior to administration, and any surplus solution is discarded immediately. This presentation summarizes computational and experimental studies of the mechanisms of glucagon fibrillation, and presents novel glucagon derivatives that resist fibrillation through phosphorylation of amino acid side chains. Phosphorylation at selected sites increases glucagon solubility at neutral pH by shifting the pI, and inhibits fibrillation through charge repulsion. On administration, the phosphate group is cleaved by ubiquitous phosphatase enzymes, regenerating native glucagon. The approach is promising for glucagon and other peptide drugs that are prone to fibrillation.

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