Identification and Characterization of a First Series of Small Molecule Inhibitors of Feline Islet Amyloid Polypeptide Aggregation

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Introduction

In a majority of diabetic cats, amyloid deposits have been detected in the islets of Langerhans. These deposits originate from islet amyloid polypeptide (IAPP), a satiety hormone produced and co-secreted with insulin by beta cells. Islet amyloid deposits have been associated with beta cell death, thus contributing to the progression of diabetes. No inhibitors of feline IAPP aggregation are currently available to stop or prevent pancreatic amyloidosis in feline diabetes mellitus. We aim to design and prepare novel small molecules to stop the formation of pancreatic amyloidosis in diabetic cats.

Methods

We prepared 155 small molecules to inhibit the aggregation of feline IAPP. Herein, we present the screening of these small molecules, focusing on one particular series (family) of about 28 molecules. The inhibition of feline IAPP fibril formation was assessed with thioflavin-T assays and confirmed with transmission electron microscopy.

Results

Based on the screening of this series of molecules, we discovered three potent inhibitors of feline IAPP aggregation which delayed the lag time: KN-21-48, NBMI-19-24, MO-19-49.

Conclusions

Identifying inhibitors of feline IAPP aggregation could yield insight into new therapeutic approaches to reduce beta cell death and slow progression of feline diabetes mellitus.