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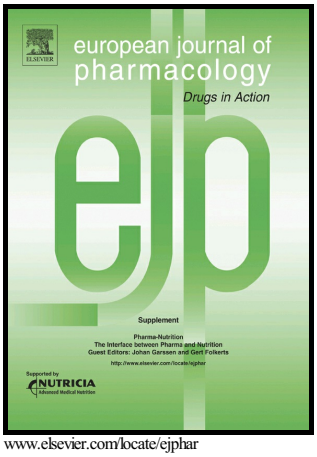

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In-vitro and in-vivo studies supporting the therapeutic potential of ZP3022 in diabetes

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Abstract:

GLP-1-gastrin dual agonist ZP3022 has been shown to increase β-cell mass with a concomitant improvement of glycemic control in diabetic mice and rats. Here we tested the in-vitro effects of ZP3022 on β-cell proliferation, islet apoptosis and glucose-stimulated insulin secretion (GSIS) in rat islets of Langerhans. Moreover, gene expression profiling in whole pancreas from Zucker Diabetic Fatty (ZDF) rats was performed to characterize genes differently regulated by short-term treatment with ZP3022. Treatments with exendin-4, gastrin-17 alone or in combination were included in the studies. ZP3022 promoted β-cell proliferation, protected from palmitate-, but not from cytokine-induced apoptosis, and induced an increase in GSIS, demonstrating a glucose dependent insulinotropic action of ZP3022 on β-cells. The combination treatment with exendin-4 and gastrin-17 showed comparable effects on proliferation, apoptosis, and GSIS as did ZP3022. Microarray analysis revealed that ZP3022 exerted specific effects on pancreatic gene expression not observed when treating ZDF rats with either exendin-4 alone or in combination with gastrin-17. In particular MAPK signaling pathway was observed among the highest affected pathways;