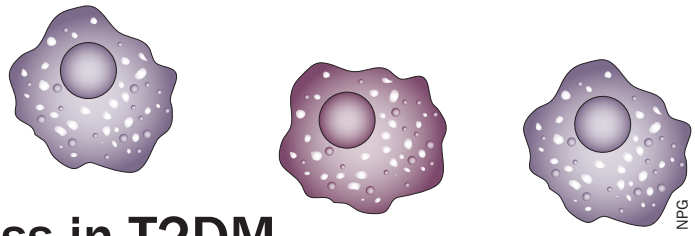
Nature Reviews Endocrinology **9**, 626 (2013); published online 10 September 2013; doi:10.1038/nrendo.2013.177



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DIABETES

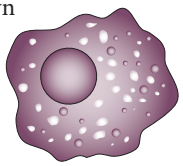
Macrophages mediate β-cell loss in T2DM

Type 2 diabetes mellitus (T2DM) is characterized by an inadequate number of β cells, which are unable to meet the increased insulin demands of the body. A recent study published in *Nature Medicine* has shown that macrophages have an important role in β-cell loss in T2DM.

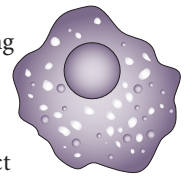
Endocannabinoids are endogenous lipid ligands that are known to promote appetite, increase peripheral lipogenesis and induce insulin resistance via activation of cannabinoid receptor 1 (CB1). Although pharmacological blockage of CB1 leads to reduced obesity and metabolic complications, the development of CB1 antagonists has been stopped as these therapeutics have been associated with undesirable neuropsychiatric adverse effects. These effects are probably caused by central activation of CB1, rather than by peripheral effects.

Both endocannabinoids and CB1 are present in β cells, but their exact role in β-cell loss has been unclear. "We used a combination of *in vivo* experiments in Zucker diabetic fatty rats to analyse hormonal and metabolic status related to T2DM. In addition, *in vitro* studies were used to explore the inflammatory mechanisms involved in β-cell death in pancreatic islets, macrophages and β cells isolated from humans and rodents," explains George Kunos, one of the principal investigators.

Blocking peripheral CB1 with JD5037, a non-brain-penetrant CB1 inverse agonist, resulted in decreased loss of β-cell function and delayed progression of T2DM. Immunohistochemical stains revealed that pancreatic islets from Zucker diabetic fatty rats were enlarged and infiltrated with $CD68^+$ macrophages that expressed the Nlrp3 inflammasome, compared with islets from lean rats. Treatment with JD5037 led to reduced macrophage infiltration and inflammasome expression. Furthermore, β-cell loss and T2DM could be reversed by inducing macrophage apoptosis or by macrophage-specific knock down of CB1.



Kunos explains that the peripheral CB1 antagonist used in this study is currently undergoing a toxicology screening to enable safety approval from the FDA as a prelude to its clinical testing in patients with T2DM.



The researchers are now exploring the signalling pathways that link CB1 to inflammasome activation in macrophages.

"These findings raise the prospect of peripheral CB1 blockade as a therapeutic approach in the treatment and, possibly, the prevention of T2DM," concludes Kunos.

Elisabeth Kugelberg

Original article Jourdan, T. *et al.* Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates β-cell loss in type 2 diabetes. *Nat. Med.* doi:10.1038/nm.3265