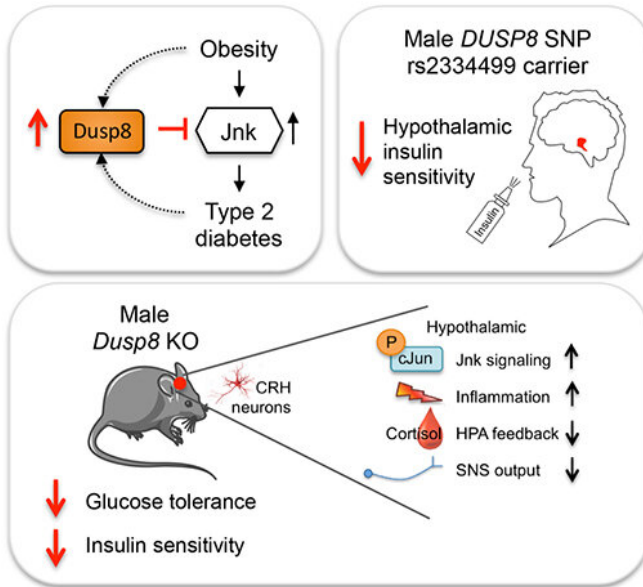


A gatekeeper against insulin resistance in the brain

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Credit: Deutsches Zentrum fuer Diabetesforschung DZD

The brain plays a major role in controlling our blood glucose levels. In type 2 diabetics this glucose metabolism brain control is often dysfunctional. Genetic components for this phenomenon have so far remained elusive. A group of scientists at Helmholtz Zentrum München and the German Center for Diabetes Research (DZD) have now shown in the *Journal of Clinical Investigations* that in men a genetic variant of the gene DUSP8 can increase the risk for type 2 diabetes by impairing our brain response to the hormone insulin.

Insulin is a pancreatic hormone that controls our blood sugar levels. Insulin not only stimulates the uptake of glucose from blood into peripheral tissues, it also acts on the brain, specifically the hypothalamus, to control glucose and energy metabolism. In obese subjects, [insulin](#) loses some of its activity due to the activation of inflammatory

signaling and a subsequent impairment of the cellular response downstream to the insulin receptor. This phenomenon, termed insulin resistance, is a major hallmark in the development of type 2 diabetes, but to date not yet fully understood. Recent genome-wide association studies (GWAS) identified DUSP8 as type 2 diabetes risk gene. Now, scientists have investigated how the protein Dusp8 (dual-specificity phosphatase 8), which is encoded by the DUSP8 gene, regulates glucose tolerance and [insulin sensitivity](#).

Genetic variant of the DUSP8 gene increases risk of type 2 diabetes

"Carriers of a genetic variant of the gene DUSP8 were shown to have a moderately increased risk for type 2 diabetes, but the functional importance of Dusp8 for the etiology of the disease remained unknown," explains Dr. Sonja C. Schriever, lead author of the study. "By combining cellular models, Dusp8 loss- and gain-of-function mice and [functional magnetic resonance](#) imaging (fMRI) of humans with genetic variants in the gene DUSP8, we now exposed a specific role of the protein Dusp8 as a gatekeeper for systemic glucose tolerance and hypothalamic insulin sensitivity," adds colleague and senior author Prof. Dr. Paul Pfluger. Within the framework of the German Center for Diabetes Research (DZD), both scientists formed a team of biologists, epidemiologists and clinicians that was able to unravel the molecular mechanisms that link Dusp8 with the development of type 2 diabetes.

Protein Dusp8 has regulatory effects on hypothalamic insulin sensitivity

The protein Dusp8 has a regulatory effect on inflammatory processes in the hypothalamus and on the hypothalamic-pituitary-adrenal (HPA) axis. It seems to protect the organism against hyper-activation of inflammatory signaling and impaired

insulin sensitivity in the hypothalamus. The scientists could show that the deletion of the *Dusp8* gene in male but not in female mice increased hypothalamic inflammation, impaired HPA axis feedback and increased basal stress hormone levels, which all together aggravated the insulin sensitivity. The sex-specific role of murine *Dusp8* was consistent with fMRI data in human volunteers that revealed reduced hypothalamic insulin sensitivity in male but not female carriers of the *DUSP8* type 2 diabetes risk variant.

"Unraveling the multi-systemic processes that drive the impaired hypothalamic insulin sensitivity in the mouse models was an important step to understand the mechanistic underpinnings of the type 2 diabetes risk gene *DUSP8*," concludes Schriever. In future studies, the researchers want to investigate the effect of central insulin action and the *DUSP8* type 2 [diabetes](#) risk variant on the hypothalamic-pituitary-adrenal axis in human subjects with or without T2D.

More information: Sonja C. Schriever et al, Type 2 diabetes risk gene *Dusp8* regulates hypothalamic Jnk signaling and insulin sensitivity, *Journal of Clinical Investigation* (2020). [DOI: 10.1172/JCI136363](#)

Provided by Deutsches Zentrum fuer
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