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Early life stress induces glucose intolerance and insulin secretion failure in elder female mice

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The incidence of metabolic disorders is increasing worldwide. Besides diet and life style habits, epidemiological studies highlighted an association between post-traumatic stress and metabolic disorders. Based on the concept of Developmental Origins of Health and Diseases our study aimed to investigate whether early life stress can trigger metabolic disorders and associated key feature i.e. low-grade inflammation.

Maternal separation (MS) is an established model of early life stress in rodent. C3H/HeN mice pups were separated from their dam and the rest of the litter 3 hours per day during 10 days starting at post-natal day 2 (PND2). All experiments were carried out in female offspring aged of PND350 on standard diet. Metabolic state was evaluated by oral glucose tolerance test (OGTT) and intraperitoneal insulin tolerance test (ITT). Cellular immune response was analyzed by primary cell culture of spleen, *lamina propria* (LP) and mesenteric lymph nodes. Immune state of liver and pancreas were evaluated through cytokine measurements by ELISA.

MS decreased body weight of female mice at PND350. MS mice developed glucose intolerance, measured during OGTT. The area under the curve (blood glucose mg/dL/2h) during OGTT was significantly increased by MS. MS did not induce a loss of insulin sensitivity measured by ITT. Instead, MS decreased fed plasma insulin levels and insulin secretion during OGTT without any modification of cytokine signature in pancreas. MS increased TNF α and TGF β concentrations in the liver. Furthermore, MS increased anti-CD3/CD28 induced secretion of IL17 and IL22 by LP cells and IFN γ by splenocytes.

For the first time, this study showed that early life stress induces glucose intolerance associated with a loss of insulin secretion in mice non-genetically predisposed to metabolic disorders or type 1 diabetes and fed with standard diet. Interestingly, glucose intolerance is associated with local (Th17 and Th22 in small intestine LP) and systemic (Th1 spleen) low-grade inflammation.