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# Genetic deletion of RAGE in Dbdb mice interferes in the liver with other AGE-receptors and AGE-detoxifying systems sustaining lipogenesis and inflammation.

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**Background and aims:** Advanced glycation end products (AGEs) are toxic compounds involved in the onset of insulin resistance in obesity. In particular, AGEs are preferentially trapped by adipose tissue through the binding with the AGE-receptor RAGE, leading to the activation of proinflammatory signalling in adipocytes that can interfere with peripheral insulin sensitivity.
The genetically-induced deletion of RAGE in leptin receptor deleted (DbDb) mice, a model of type 2 diabetes/obesity, is reported to prevent AGEs trapping in adipocytes, paralleled by increased circulating levels of AGEs, and reduced adipose tissue inflammation and insulin resistance. Since this might increase the exposition to AGEs of highly perfused organs, such as the liver, we aimed to analyze whether the deletion of RAGE affected hepatic AGEs accumulation and detoxification in the liver of obese/diabetic animals.
**Materials and methods:** At 13 weeks of age, wild-type C57, DbDb and DbDb RAGE-/- mice were sacrificed, plasma was collected and liver was removed. Gene and protein expression of AGEs receptors and detoxifying systems were analyzed in parallel to hepatic AGEs content, activation of lipogenesis, and markers of inflammation.
**Results:** The deletion of RAGE in the liver of DbDb mice was associated with decreased expression of AGE-receptor-1 ($P$<0.05 vs. DbDb) and reduced expression and activity of glyoxalase-1 ($P$<0.01 vs. DbDb), two major AGEs detoxifying systems, and increased galectin-3 expression ($P$<0.05 vs. DbDb), another AGEs-receptor. The latter may be a compensatory response to remove plasma AGEs. Thus, despite the lacking of RAGE, high levels of intrahepatic AGEs were maintained in DbDb RAGE-/- mice, due to either the trapping exerted by galectin-3 and/or the reduced potential of detoxifying systems. These alterations were also associated to persistent activation of the SREBP1c lipogenic pathway ($P$<0.001 vs. C57), and the proinflammatory NLRP3 signaling pathway ($P$<0.05 vs. C57), that were not prevented by RAGE deletion compared to DbDb mice.
**Conclusion:** RAGE deletion in the liver of an animal model of type 2 diabetes influences other AGE-receptors and AGE-detoxifying systems. In particular, the increase in galectin-3 in DbDb RAGE-/- mice liver might be responsible for the sustained hepatosteatosis and inflammation. This complex mechanism of control should be taken into account when investigating on the pathogenic contribution of AGEs to hepatic obesity/diabetes complications.