Genetic deletion of RAGE in Dbdb mice interferes with AGEs receptors and detoxifying systems in liver.

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Advanced glycation end products (AGEs) are toxic compounds involved in the development of diabetes complications and 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 signaling and oxidative stress in adipocytes that can interfere with peripheral insulin sensitivity. The genetically-induced deletion of RAGE in leptin receptor deleted (DbDb) mice, a model of diet-induced diabetes/obesity, is reported to increase circulating AGEs levels and reduce adipose tissue inflammation and insulin resistance. However, we here report that the deletion of RAGE in DbDb mice, in contrast to other tissues, impairs hepatic AGE-receptor-1 and glyoxalase-1, two major AGEs detoxifying systems, and increases galectin-3 expression, another AGEs-receptor, as a compensatory response to remove plasma AGEs that might sustain hepatosteatosis and inflammation. These results thus indicate a complex tissue specific control mechanism among AGEs receptors and detoxifying systems that need to be better elucidated to identify molecular targets and therapeutic tools to modulate the pathogenic contribution of AGEs to hepatic metabolic disturbances.