Does junk food steal memories?

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Obesity, a multifactorial metabolic disorder, is rapidly increasing in western and developing countries. Nearly 35% of adults over the age of 20 and 50% of adults over the age of 60 have a metabolic syndrome, which may lead to serious health problems. In fact, we consume more food than necessary and this food is usually far from being healthy. Indeed, life style and education shape the direction in which humanity is going globally.

Interestingly, factors associated with metabolic syndromes negatively

impact cognition and thus represent serious risk factors for dementia and intellectual disabilities (Yaffe K et al., 2004). In fact, "junk food", which is food mostly enriched in sugar and fat (I know, we often crave it), strongly disrupts learning and memory functions in both humans and rodents. Given that obesity is epidemic and tied to impaired cognition, understanding the long-term impact of a high-fat diet (HFD) on the hippocampus –a key brain structure involved in learning and memory processes– is of paramount importance, especially in children and adolescents.

In a recent PLOS ONE article, Catrina Sims-Robinson and colleagues from the Medical University of South Carolina decided to investigate the impact of HFD hippocampal functions and whether dietary reversal may rescue short- and long-term alterations (Sims-Robinson et al., 2016). As part of this study, mice were exposed either to normal food or to high-fat food for several days –just imagine something like a diet based on tasty, saucy, fat burgers for weeks and weeks. Using hippocampus-dependent behavioral paradigms, such as the Novel Object Recognition (NOR) and the Morris Water Maze (MWM) tests, the authors observed that obese mice exhibited severe memory loss. Obese mice were indeed unable to discriminate between objects or to simply recall spatial references; basically, they were lost. Interestingly –and luckily– such deleterious effects of a high-fat diet on memory processes were entirely abolished once mice were re-exposed (dietary reversal) to a normal and healthy diet, which strongly indicates that cognitive dysfunctions induced by "junk food" may be somehow reversible.

In order to go a bit further in dissecting the cellular and molecular mechanisms possibly underlying "junk food"-induced cognitive decline, the authors focused on the insulin signaling pathway and its cerebral receptors. The notion that insulin, a hormonal peptide secreted by the pancreas, could act on the brain might come as a surprise; as such, this study constitutes a fascinating piece of science. In fact, insulin, like

many other peripheral peptides (leptin, ghrelin, GLP-1, etc), can send a plethora of information to our brain, thus influencing our behavior.

HFD is associated with peripheral insulin resistance, which occurs following hyperinsulinemia and InsR (Insulin Receptor) desensitization (Draznin, 2006). At the central level, HFD is associated with insulin resistance in various critical brain regions, including the hypothalamus, cortex and hippocampus; however, whether these dramatic changes are reversible remains elusive. In fact, "this is the first study, to our knowledge, that reports an improvement in impaired hippocampal insulin signaling and an irreversible decrease InsR expression in the hippocampus with dietary intervention", said the authors. "It is possible that the reduction in InsR expression in the hippocampus following a HFD is a protective mechanism to prevent over activation of insulin signaling and subsequent desensitization", concluded Catrina Sims-Robinson, the leading author of the study. Hence, it could be possible that HFD may lead to an acceleration of age-related decrease in InsR expression. Although further studies are definitely warranted, this may represent a factor in the increased risk of age-related neurodegenerative diseases (i.e. Alzheimer's disease and dementia) in metabolic syndromes.

It is likely that several molecular pathways are involved in the mechanisms underlying diet-induced changes on cognition and among them insulin may play a critical role. In this study, Dr. Sims-Robinson and colleagues demonstrate that dietary intervention (dietary reversal) improves impaired glucose tolerance, impaired hippocampal insulin signaling, and cognitive deficits, even though the reduction in the levels of the InsRs was irreversible. It must be mentioned that hippocampal-dependent cognitive deficits induced by HFD have been attributed also to leptin, calcium dysregulation, inflammation, cellular stress, and impaired insulin signaling. It is therefore difficult to point to a single factor entirely responsible for such a mess within the hippocampus. Nonetheless the authors added that "enhancing insulin signaling has

promising therapeutic benefits for improving cognition; however, more research is needed to understand its impact on endoplasmic reticulum stress and inflammation".

In conclusion, this research should encourage a more detailed investigation of the secrets of our brain, as well as to strive for a deeper understanding of what food does to our mental functions. In the meantime, a healthy lunch may be the easiest solution to please and protect our brain.

More information: Catrina Sims-Robinson et al. Dietary Reversal Ameliorates Short- and Long-Term Memory Deficits Induced by High-fat Diet Early in Life, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0163883