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# A mechanism for the development of obesity-associated conditions

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Substances known as endocannabinoids have been implicated in the development of many effects of a high-fat diet, including risk factors for type 2 diabetes. New data have now indicated that these effects of endocannabinoids occur via activation of the protein CB1 in the liver and not the brain. Therefore, targeting liver CB1 might provide an effective way to treat obesity-related medical conditions without the side effects of targeting CB1 in the brain, anxiety and depression.

Endocannabinoids are substances produced by several cells in the body that are very similar to compounds found in cannabis plants. They have been implicated in the development of many effects of a high-fat diet, including many risk factors for type 2 diabetes: obesity, insulin resistance, leptin resistance, and dyslipidemia.

It is important to determine whether these effects of endocannabinoids occur via activation of the protein CB1 in the brain, liver, or other tissues, as the therapeutic potential of agents that target CB1 is currently limited by the side effects of targeting CB1 in the brain, anxiety and depression. However, new insight into this issue has now been provided by George Kunos and colleagues, at the National Institutes of Health, Rockville, through analysis of mice lacking CB1 only in the liver.

Similar to normal mice, when the mice lacking CB1 only in the liver were fed a high-fat diet they became obese. However, they exhibited less severe insulin resistance, leptin resistance, and dyslipidemia than the normal mice. They also exhibited less severe high fat diet–induced fatty

liver, something that increases the risk of developing cirrhosis of the liver.

The data indicate that high fat diet–induced obesity is influenced by CB1 found in tissues other than the liver and that liver-specific CB1 is necessary for the development of high fat diet–induced fatty liver and the hormonal and metabolic changes that occur as a result of such a diet, increasing the risk of type 2 diabetes. The authors therefore suggest that targeting liver CB1 might provide an effective way to treat obesity-related medical conditions without the side effects of targeting CB1 in the brain.

Source: Journal of Clinical Investigation