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Triglycerides induce leptin resistance at the blood-brain barrier.

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Abstract

Obesity is associated with leptin resistance as evidenced by hyperleptinemia. Resistance arises from impaired leptin transport across the blood-brain barrier (BBB), defects in leptin receptor signaling, and blockades in downstream neuronal circuitries. The mediator of this resistance is unknown. Here, we show that milk, for which fats are 98% triglycerides, immediately inhibited leptin transport as assessed with in vivo, in vitro, and in situ models of the BBB. Fat-free milk and intralipid, a source of vegetable triglycerides, were without effect. Both starvation and diet-induced obesity elevated triglycerides and decreased the transport of leptin across the BBB, whereas short-term fasting decreased triglycerides and increased transport. Three of four triglycerides tested intravenously inhibited transport of leptin across the BBB, but their free fatty acid constituents were without effect. Treatment with gemfibrozil, a drug that specifically reduces triglyceride levels, reversed both hypertriglyceridemia and impaired leptin transport. We conclude that triglycerides are an important cause of leptin resistance as mediated by impaired transport across the BBB and suggest that triglyceride-mediated leptin resistance may have evolved as an anti-anorectic mechanism during starvation. Decreasing triglycerides may potentiate the anorectic effect of leptin by enhancing leptin transport across the BBB.

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Publication Types, MeSH Terms, Substances, Grant Support

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MeSH Terms

Animals
Biological Transport/drug effects
Blood-Brain Barrier/drug effects*
Blood-Brain Barrier/physiology*
Drug Resistance
Fat Emulsions, Intravenous/pharmacology
Gemfibrozil/pharmacology
Hypertriglyceridemia/blood
Hypolipidemic Agents/pharmacology
Leptin/metabolism
Leptin/physiology*
Male
Mice
Mice, Inbred Strains
Milk
Triglycerides/antagonists & inhibitors
Triglycerides/blood
Triglycerides/pharmacology*

Substances

Fat Emulsions, Intravenous
Hypolipidemic Agents
Leptin
Triglycerides
Gemfibrozil

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