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Antisense oligodeoxynucleotides to G-protein Î±-subunit subclasses identify a transductional requirement for the modulation of normal feeding dependent on $G\hat{I}\pm_{OA}$ subunit

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Abstract

A variety of G-protein-coupled receptors are proposed to participate in the modulation of ingestive behavior and in the mode of action of antiobesity drugs. In the present study, we investigated the involvement of G-protein Î±-subunit subclasses (molecular transducers of multiple chemical signals) in the control of ingestive behavior. We report here that the chronic intracerebroventricular (i.c.v.) microinfusion for 72 h (via osmotic minipumps) with antisense phosphothio-oligodeoxynucleotides corresponding to G-protein $\hat{I}\pm\text{-subunit}_{O\ common}$ (to$_{OA}$ and$_{OB}$) and$_{OA}$ subclasses decrease the nighttime food

intake without affecting water intake in rats. Computerized analyses of the microstructure of feeding indicate that the GÎ±$_{OA}$ antisense depresses feeding by reducing meal frequency, while meal size and meal duration increased slightly, but not significantly. The effects of GÎ±$_{O\ common}$ and GÎ±$_{OA}$ antisense on feeding are specific since the chronic i.c.v. microinfusion of sense to GÎ±$_{O\ common}$ or GÎ±$_{OA}$, antisense to the related subclass GÎ±$_{OB}$, and antisense to other G-protein Î±-subunits (GÎ±$_{S}$, GÎ±$_{Q}$, GÎ±$_{11}$ and GÎ±$_{i\ common}$) had no effect on food or water intake. The observed effects by GÎ±$_{O\ common}$ and GÎ±$_{OA}$ antisense imply a direct action in the central nervous system since the chronic subcutaneous microinfusion of GÎ±$_{O\ common}$ and GÎ±$_{OA}$ antisense in doses equivalent or two-fold higher relative to those administered centrally had no effect on food intake. The chronic microinfusion of GÎ±$_{O\ common}$ antisense drastically decreased the levels of GÎ±$_{O}$ protein detected in immunoblots of hypothalamic ventromedial nuclei. The results suggest that the G-protein Î±-subunit subclass GÎ±$_{OA}$ is critical for the integrative modulation of normal feeding behavior, and that changes in its activity may be associated with modifications of feeding. These studies also show a novel approach to study the molecular basis of specific behaviors by manipulating elements of the transductional systems.

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Keywords

Antisense oligonucleotide; G-protein; Feeding; Food intake; Meal pattern; Anorexia; Nervous system; Intracerebroventricular administration; Rat

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