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Resumo	In outbred mice, susceptibility or resistance to diet-induced obesity is associated with rapid changes in hypothalamic proopiomelanocortin (POMC) levels. Here, we evaluated 3 hypotheses that potentially explain the development of the different obesity phenotypes in outbred Swiss mice. First, rapid and differential changes in the gut microbiota in obesity-prone (OP) and obesity-resistant (OR) mice fed on a high-fat diet (HFD) might cause differential efficiencies in fatty acid harvesting leading to changes in systemic fatty acid concentrations that in turn affect POMC expression and processing. Second, independently of the gut microbiota, OP mice might have increased blood fatty acid levels after the introduction of a HFD, which could affect POMC expression and processing. Third, fatty acids might act directly in the hypothalamus to differentially regulate POMC expression and/or processing in OP and OR mice. We evaluated OP and OR male Swiss mice using 16S rRNA sequencing for the determination of gut microbiota; gas chromatography for blood lipid determination; and immunoblot and real-time polymerase chain reaction for protein and transcript determination and indirect calorimetry. Some experiments were performed with human pluripotent stem cells differentiated into hypothalamic neurons. We did not find evidence supporting the first 2 hypotheses. However, we found that in OP but not in OR mice, palmitate induces a rapid increase in hypothalamic *POMC*, which is followed by increased expression of proprotein convertase subtilisin/kexin type 1 *PC1/3*. Lentiviral inhibition of hypothalamic *PC1/3* increased caloric intake and body mass in both OP and OR mice. In human stem cell-derived hypothalamic cells, we found that palmitate potently

	suppressed the production of POMC-derived peptides. Palmitate directly regulates *PC1/3* in OP mice and likely has a functional impact on POMC processing.
Fomento	