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Review

# Lipid sensing in the brain and regulation of energy balance

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**Abstract**

Nutrient-sensitive neurons [to glucose and fatty acids (FAs)] are present at many sites throughout the brain, including the hypothalamus and brain stem, and play a key role in the neural control of energy and glucose homoeostasis. Through their neuronal output, FAs can modulate feeding behaviour as well as insulin secretion and activity. Central administration of oleate, for example, inhibits food intake and glucose production in rats. This suggests that daily variations in plasma FA concentrations could be detected by the central nervous system as a signal that contributes to regulation of energy balance. At the cellular level, subpopulations of neurons in the ventromedial and arcuate hypothalamic nuclei are selectively either inhibited or activated by FAs. Possible molecular effectors of these FA effects most likely include the chloride and potassium ion channels. While intracellular metabolism and activation of the ATP-sensitive $K^+$ channels appear to be necessary for some signalling effects of FAs, at least half the FA responses in ventromedial hypothalamic neurons are mediated by interaction with fatty acid translocase (FAT)/CD36, an FA transporter/receptor that does not require intracellular metabolism to activate downstream signalling. Thus, FAs and their metabolites can modulate neuronal activity by directly monitoring the ongoing fuel availability for brain nutrient-sensing neurons involved in the regulation of energy and glucose homoeostasis. Besides these physiological effects, FA overload or metabolic dysfunction may also impair neural control of energy homoeostasis and contribute to obesity and/or type 2 diabetes in predisposed subjects.


*Keywords:* Hypothalamus; FAT/CD36; Potassium channel; Energy balance

## 1. Introduction

The central nervous system (CNS) is a key player in the regulation of energy balance in mammals [1]. The process involves a combination of signals arising from the periphery, including hormones (such as leptin, insulin and ghrelin) and nutrients [glucose and fatty acids (FAs)], detected by specialized brain areas like the hypothalamus and brain stem [2,3]. Since the work by Oomura et al. [4], there is growing evidence suggesting that hypothalamic FA sensing plays a role in the regulation of energy balance, including insulin secretion and activity, hepatic glucose production, linear growth, adipose deposition and food intake [5–8]. The molecular mechanisms involved in this FA sensing by the brain are still a matter of debate, but they may well include plasma membrane proteins such as fatty acid translocase (FAT)/CD36 as well as intracellular events involving acyl-coenzyme A (CoA) synthase and FA oxidation [9]. In addition, recent studies have highlighted the role of neuronal lipoprotein lipase (LPL)-mediated hydrolysis of triglyceride (TG)-enriched particles in the regulation of energy balance [10].

The present report is a review of the mechanisms of lipid actions in CNS areas controlling energy homoeostasis (with a focus on the hypothalamus) at molecular, cellular and systems levels under physiological conditions. Furthermore, deregulation of brain FA sensing may contribute to further deterioration of energy balance and ultimately to obesity, with or without type 2 diabetes as a complicating factor [11]. A better understanding of these mechanisms, and further characterization of FA-sensitive neurons and their role in physiological and pathological processes could lead to the identification of novel pharmacological targets for the prevention and treatment of diabetes and obesity.

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## 2. Transport of FAs to the brain and neurons

Cerebral lipids are an essential component of both membranes and intracellular signalling pathways. They represent 50% of brain dry weight, the highest organ lipid content after adipose tissue [12,13]. A growing body of evidence suggests that cerebral lipids are derived by both local synthesis and uptake from the blood circulation. Several studies show that some polyunsaturated FAs (PUFAs) have the ability to cross the blood–brain barrier (BBB) [14,15]. Once across the BBB, it is likely that neurons then take up FAs, as some neurons appear to have FA transporters. Dissociated neurons from the hypothalamic ventromedial nucleus (VMN) of rats, for example, express mRNA for FA transport proteins (FATP)-1 and -4 and for the FA transporter/receptor FAT/CD36 [7,16]. In addition, while it is unlikely that neurons derive much of their energy supply from FAs, these same neurons express mRNA for intracellular FA metabolism such as long-chain acyl-CoA synthase (ACS), carnitine palmitoyltransferase-1A and -1C (CPT1A/1C), and uncoupling protein 2 (UCP2) [16]. They also express enzymes for *de novo* FA synthesis such as FA synthase (FAS) [16]. However, it is likely that much of the reported oxidation of FAs such as palmitate in the brain probably takes place in astrocytes [17], whereas other FAs such as arachidonate are largely incorporated into phospholipids [14]. Interestingly, lipoprotein lipase (LPL) has recently been demonstrated to play a role in the regulation of energy balance by neurons [18]. The role of LPL in the brain is to convert triglyceride (TG)-rich lipoproteins into FA locally, thereby providing an indication of the metabolic state to FA-sensitive neurons [10].

## 3. Some hypothalamic neurons are lipid-responsive

Over the past decade, there has been growing evidence to demonstrate that hypothalamic FA sensing is critical for the regulation of food intake as well as insulin secretion, hepatic glucose production and lipogenesis [9]. A 6-h intracerebroventricular (ICV) infusion of the monounsaturated FA oleic acid (OA) reduced both food intake and hepatic glucose production (HGP) [8], while reducing hypothalamic FA oxidation by inhibition of CPT1 mimicked the effects on food intake and HGP induced by ICV infusion of OA [19]. In another study, direct bilateral infusion of OA into the mediobasal hypothalamus decreased HGP [20]. However, ICV and direct infusions of FA into the brain are not physiological. Interfering with FA oxidation is more likely to have a major effect on astrocyte than neuronal metabolism [21]. They could even produce non-specific effects by evoking an inflammatory response by irritating the ependymocytes and tanycytes lining the ventricles or exciting the microglia and astrocytes in the brain parenchyma.

Other, more physiological routes include raising systemic levels of FAs or infusing them directly into the carotid arteries, the primary route by which FAs reach the forebrain. In fact, a two-fold increase in plasma TG produced by a 2-day systemic infusion of TG emulsion was associated with decreased sympathetic activity [22]. The reduced sympathetic tone, which can also result from central FA infusions [22], could contribute to the associated FA-induced exaggeration of glucose-induced insulin secretion (GIIS), a condition similar to what happens in the prediabetic state [22]. In addition, this exaggerated GIIS and reduction in HGP have been mimicked by infusing TG into the carotid artery [5], but were decreased by central inhibition of CPT1 [22]. Similarly, central inhibition of CPT1 has been associated with an increase in the acyl-CoA intracellular pool postulated to be the 'final' satiety signal rather than the FAs themselves [23].

Nevertheless, there are at least two potential problems involved in the interpretation of such data *in vivo*. First, the idea that increases in brain FA levels act as a satiety signal to inhibit feeding [19] is counter-intuitive, given the fact that plasma FA levels do not rise substantially after food ingestion, but instead rise significantly during fasting, a setting in which food intake would be expected to increase [24]. Second, the vast majority of FA oxidation in the brain takes place in astrocytes rather than neurons [17]. While a selected group of neurons in the hypothalamus clearly respond directly to changes in ambient FA levels by altering their activity [4,7,16], only a relatively small percentage of these responses depend on neuronal FA metabolism [16]. Furthermore, although β-oxidation and the formation of malonyl-CoA and FA metabolites such as acyl-CoA may be mediators of the effects produced by FA infusions *in vivo* [25], it is likely that these mostly occur at the level of the astrocyte. If so, then there must be a mechanism by which alterations in astrocyte FA metabolism can provide a signal to those neurons that regulate HGP and food intake. Thus, it may be proposed that the communication between astrocyte FA metabolism and neuronal FA sensing involves the production and export of ketone bodies from astrocytes and their subsequent uptake by neurons [17].

## 4. Molecular mechanisms of neuronal FA sensing

In FA-sensitive neurons, exposure to long-chain FAs can alter the activity of a wide variety of ion channels such as $Cl^-$, $GABA_A$ [26], potassium, $K^+$-$Ca^{2+}$ [27] and calcium channels [28]. OA activates arcuate nucleus proopiomelanocortin (ARC POMC) neurons by inhibiting ATP-sensitive $K^+$ ($K_{ATP}$) channel activity, and the effect of OA on HGP is abolished by ICV administration of a $K_{ATP}$-channel inhibitor [29]. Using electrophysiological approaches *in vivo* and *in vitro*, OA-sensitive neurons have been characterized using whole-cell patch-clamp recordings in ARC slices from 14- to 21-day-old rats [30]. In these experiments, the vehicle was artificial cerebrospinal fluid (aCSF) with added β-cyclodextrin (complexed with OA) [30]. In these neurons, 13% were excited by OA and 30% were inhibited by OA [30]. The excitatory effects of OA appeared to be due to the closure of chloride channels, thus leading to membrane depolarization and increased action potential frequency [30]. On the other hand, OA inhibitory effects might involve the $K_{ATP}$ channels as such inhibition was reversed by the $K_{ATP}$-channel blocker tolbutamide [30]. Using fura-2 $Ca^{2+}$ imaging of dissociated neurons from the VMN, it was found that OA excited up to 43%, and inhibited up to 29%, of all VMN neurons independent of glucose concentrations [16]. However, in these neurons, inhibition of the $K_{ATP}$ channel mediated FA sensing in only a