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Brain lipid sensing and the neural control of energy balance

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ABSTRACT

Fatty acid (FA) -sensitive neurons are present in the brain, especially the hypothalamus, and play a key role in the neural control of energy and glucose homeostasis including feeding behavior, secretion insulin and action. Subpopulations of neurons in the arcuate and ventromedial hypothalamic nuclei are selectively either activated or inhibited by FA. Molecular effectors of these FA effects include ion channels such as chloride, potassium or calcium. In addition, at least half of the responses in the hypothalamic ventromedial FA neurons are mediated through interaction with the FA translocator/receptor, FAT/CD36, that does not require metabolism to activate intracellular signaling downstream. Recently, an important role of lipoprotein lipase in FA detection has also been demonstrated not only in the hypothalamus, but also in the hippocampus and striatum. Finally, FA could overload energy homeostasis via increased hypothalamic ceramide synthesis which could, in turn, contribute to the pathogenesis of diabetes of obesity and/or type 2 in predisposed individuals by disrupting the endocrine signaling pathways of insulin and/or leptin.

1. Introduction

The central nervous system (CNS) plays a key role in the regulation of energy balance in mammals (Luquet and Magnan, 2009). Indeed signals conveyed from the periphery via hormones (leptin, insulin, ghrelin etc.) and nutrients (glucose and fatty acids) are detected by specialized neurons in areas like the hypothalamus and brainstem (Blouet and Schwartz, 2010; Lam et al., 2005a,b; Levin et al., 2011). Among these informative molecules there is increasing evidence highlighting hypothalamic fatty acid (FA) sensing as an important contributor to the regulation of energy balance. Oomura et al. were among the first to show that some neurons in lateral hypothalamus were sensitive to FA (Oomura et al., 1975). Since then, others have confirmed a role for central FA sensing in the regulation of facets of energy and glucose homeostasis such as food intake, insulin secretion and action, hepatic glucose production, linear growth, and adipose deposition (Cruciani-Guglielmacci et al., 2004; Lam et al., 2005a,b; Le Foll et al., 2013, 2014; Obici et al., 2002). The molecular mechanisms involved in this neuronal FA sensing are still under active investigation. Some documented mechanisms include intracellular events including acylCoA synthase and FA oxidation (Migrenne et al., 2011) and the plasma membrane translocator/receptor FAT/CD36 (CD36) (Le Foll et al., 2013, 2014; Moulle et al., 2013). Recent studies have highlighted a role for neuronal lipoprotein lipase (LPL)-mediated hydrolysis of triglycerides (TG)-enriched particles in the regulation energy balance (Wang et al., 2011) in the hippocampus (Picard et al., 2013) and mesolimbic structures (Cansell et al., 2014). Here we will review the molecular, cellular and systemic mechanisms of lipid actions on CNS areas controlling the physiological regulation of energy homeostasis, with a focus on the hypothalamus. In addition, we will review the evidence that dysregulation of brain FA sensing may contribute to the deterioration of energy balance and development of obesity, with or without type 2 diabetes (Velloso and Schwartz, 2011; Yue and Lam, 2012) through ceramide-dependent effects (Contreras et al., 2014). A better understanding of these mechanisms, as well as further characterization of FA sensitive neurons and their role in physiological and pathological processes, may lead to identification of novel pharmacological targets for the prevention and treatment of obesity and diabetes.

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1.1. Transport of FA into the brain and evidence for hypothalamic FA sensitive neurons

Brain has the highest lipid content of any organ except for adipose tissue and cerebral lipids are essential components of both membranes and intracellular signaling pathways (Edmond, 2001; Watkins et al., 2001). Cerebral lipids are derived both from local synthesis and uptake from the bloodstream. Several studies show that some polyunsaturated FA (PUFA) are able to cross the blood–brain barrier (BBB) (Rapoport et al., 2001; Smith and Nagura, 2001). While still poorly understood, some mechanisms for the transport of FA from the bloodstream into the CNS have been identified. For example, a role for Mfsd2a (major facilitator superfamily domain-containing 2a) has recently been identified as a major carrier absorption of DHA in the brain (Nguyen et al., 2014). Also, FA binding proteins (FABPs) 3, 4 and 5 mRNA and protein are expressed in immortalized human brain endothelial cells (hCMEC/D3) (Lee et al., 2015). Once they have crossed the BBB, FA are avidly taken up and oxidized, mainly by astrocytes (Escartin et al., 2007). Many other FA such as arachidonate are largely incorporated into phospholipids in both neurons and astrocytes (Rapoport et al., 2001). Ventromedial hypothalamic nucleus (VMN) neurons and astrocytes can also presumably take up FA since they express mRNA for FA transport proteins (FATP)-1 and 4 and CD36 (Le Foll et al., 2013, 2014; Le Foll et al., 2009). Genes for the intracellular metabolism of FA, such as long chain acyl-CoA synthase (ACS), carnitine palmitoyltransferase-1a and 1c (CPT1a and 1C) and uncoupling protein-2 (UCP2), are also expressed in VMN neurons, although it is unlikely that neurons derive much of their energy supply from FA (Le Foll et al., 2009). In addition, VMN neurons also express enzymes for *de novo* FA synthesis such as FA synthase (FAS) (Le Foll et al., 2009). Finally, lipase (LPL), which is highly expressed in the brain (Ben-Zeev et al., 1990), could provide a signal of the metabolic state to FA sensitive neurons by converting locally triglyceride (TG)-rich lipoproteins into FA (Wang and Eckel, 2012). Interestingly, neuronal specific deletion of LPL has been demonstrated to play a role in the regulation of energy balance (Picard et al., 2013; Wang et al., 2011).

Several decades ago Oomura et al. demonstrated that FA activated lateral hypothalamic neurons (Oomura et al., 1975). In FA sensitive neurons, exposure to long chain FA can alter the activity of a wide variety of ion channels including Cl^-, $GABA_A$ (Tewari et al., 2000), potassium, K^+–Ca^{2+} (Honen et al., 2003) or Ca^{2+} channels (Oishi et al., 1990). Oleic acid (OA) sensitive-neurons have been characterized using whole cell patch clamp records in arcuate nucleus (ARC) slices from 14 to 21 day old rats as well as *in vivo* recording using implanted microelectrode (Wang et al., 2006). Of all ARC neurons sampled, 13% were excited and 30% were inhibited by OA (Wang et al., 2006). The excitatory effects of OA appeared to be due to closure of chloride channels leading to membrane depolarization and increased action potential frequency (Wang et al., 2006). On the other hand, the inhibitory effect of OA may involve K_{ATP} channels since this inhibition was reversed by the K_{ATP} channel blocker tolbutamide (Wang et al., 2006). Using fura-2 calcium imaging in dissociated VMN neurons, OA excited up to 43% and inhibited up to 29% of all VMN neurons independently of glucose concentrations (Le Foll et al., 2009). However, in these neurons, inhibition of the K_{ATP} channel mediated FA sensing in only a small percentage of FA sensing neurons. The differences between the findings *in vivo* and *in vitro* using electrophysiological methods and individual dissociated neurons using calcium imaging are likely due to the additional presynaptic inputs to the neurons assessed by electrophysiological methods and the fact that the drugs used affect both neurons and astrocytes in slice preparations *in vivo*. In addition, although a relatively large percentage of hypothalamic neurons are FA sensors, a select population also sense glucose and their responses to FA are highly dependent upon ambient glucose concentration (Le Foll et al., 2013, 2014; Le Foll et al., 2009; Migrenne et al., 2006). Such data suggest that the responses of hypothalamic FA sensitive neurons are dependent upon the metabolic state of the animal and thus might be expected to respond differently during fasting (when FA levels rise and glucose levels fall) vs. the overfed state when glucose levels rise while free FA levels remain relatively unchanged (Le Foll et al., 2013, 2014; Le Foll et al., 2009; Migrenne et al., 2006).

1.2. FA fate in sensitive neurons

While intracellular FA metabolism may be responsible for altering neuronal activity in some FA sensitive neurons, such as ARC POMC neurons (Jo et al., 2009), it accounts for a relatively small percent of the excitatory or inhibitory effects of OA on dissociated VMN neurons (Le Foll et al., 2013, 2014; Le Foll et al., 2009). In those neurons, inhibition of CPT1, reactive oxygen species formation, long-chain acylCoA synthetase and K_{ATP} channel activity or activation of uncoupling protein 2 (UCP2) account for no more than 20% of the excitatory or approximately 40% of the inhibitory effects of OA (Le Foll et al., 2009). On the other hand, inhibition of CD36 which can alter cell function independently of intracellular FA metabolism, reduced the excitatory and inhibitory effects of OA on FA-glucose sensitive neurons by up to 77% in FA-excited and completely abolished OA effects on FA inhibited neurons (Le Foll et al., 2013, 2014; Le Foll et al., 2009). Thus, in most VMN FA sensing neurons, CD36 may act primarily as receptor for long chain FA as it does on taste cells on the tongue where it activates store-operated calcium channels to alter membrane potential and release of serotonin (Gaillard et al., 2008). These effects all occur in the presence of nanomolar concentrations of OA in dissociated neurons (Le Foll et al., 2009), whereas micromolar concentrations are generally required to effect similar changes in neuronal activity in brain slice preparations (Jo et al., 2009; Migrenne et al., 2006; Wang et al., 2006). Thus, in the absence of astrocytes and presynaptic inputs, OA can directly affect VMN neuronal activity through both metabolic and non-metabolic pathways. Alternatively, FA might act as signaling molecules by covalent attachment to proteins (N-terminal acylation) to alter the function of membrane and intracellular signaling molecules. For example, palmitoylation facilitates the targeting and plasma membrane binding of proteins which otherwise would remain in the cytosolic compartment (Resh, 1999). Some membrane proteins (TGFα, a 25 kDa synaptosomal-associated protein which is required for exocytosis) and plasma membrane receptors (seven transmembrane G-protein-coupled receptors such as α_{2a}- and β_2-adrenoceptors) are typically palmitoylated on one or several cysteine residues located adjacent to or just within the transmembrane domain (Resh, 1999). Such mechanisms might also modulate neuronal FA sensing. It may also be possible that certain fatty acids might alter neuronal activity by binding to GPR120 receptors. However, although these receptors are expressed in the rHypoE-7 hypothalamic cell line (Wellhauser and Belsham, 2014), mRNA for GRP120 is not expressed in VMN neurons (LeFoll et al.).

1.3. Which neurotransmitters or neuropeptides?

The final consequence of the activation or inactivation of a neuron is the release of neurotransmitters and neuropeptides. Since FA decrease food intake, they might be expected to alter the activity of neurons specifically involved in the regulation of feeding. For example, OA activates ARC POMC neurons in mice by inhibiting ATP-sensitive K^+ (K_{ATP}) channel activity and the effect of OA on HGP