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Review Article

Reactive oxygen species signaling influences feeding behaviour

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ABSTRACT

Reactive Oxygen Species (ROS) are not just by products of substrate oxidation but also chemicals that are involved in intracellular signaling when they are generated transiently and moderately. This review explores the intracellular signaling aspects of reactive oxygen species in influencing feeding behaviour. Substrates like glucose and lipids stimulate generation of reactive oxygen species mainly through mitochondria and to some extent through the NADPH oxidases. The level of ROS generated in hypothalamic neurons like NPY/AgRP and POMC neurons, under the influence of substrate level, directly influences the activity of these neurons and subsequently affect the downstream neurons located in other parts of the hypothalamus like the ventromedial nucleus (VMN), the paraventricular nucleus (PVN) and the lateral hypothalamus. Activation of POMC neuronal population is driven by increase ROS level whereas activation of NPY/AgRP neurons occurs when ROS level is reduced. The activation of these neurons will determine the feeding behaviour which will either be satiety if POMC neurons are activated or increase food intake if NPY/AgRP neurons are activated.

Keywords: Agouti related peptide (AgRP), Feeding behaviour, Neuro-peptide Y (NPY) neurons, Pro-opiomelanocortin (POMC) neurons, Reactive oxygen species (ROS)

INTRODUCTION

The term Reactive Oxygen Species (ROS) refers to numerous molecules and free radicals, which are chemical species with one impaired electron derived from molecular oxygen. Most tissues produce Reactive Oxygen Species (ROS) continuously as by products of substrate oxidation. However, the production of ROS is also important for redox signaling in physiology and pathology, in the cellular oxygen- sensing cascade, in phagocytosis and in the mechanism of nutrient sensing, especially glucose sensing.

ROS are generated by all cellular processes utilizing oxygen, and mitochondrial transport electron chain is the main source.[1] ROS are also generated by NADPH oxidases (NOX) or gp91[2,3] which was first discovered in and cloned from neutrophilic granulocytes. Other sources of ROS are the endoplasmic reticulum[4] and peroxisome.[5] Synaptosomes have also been implicated in the formation of ROS especially O_2^- by an enzyme ketoglutarate dehydrogenase.[6]

Overproduction of ROS can be deleterious and lead to free radical mediated chain reactions which targets protein, lipid, polysaccharides and DNA, and eventually lead to deterioration of various tissues and organs.[7] But

when ROS are generated moderately and transiently they participate in intracellular signaling as signal molecules.[7] Ordinarily, excess ROS are scavenged by various enzymatic and non-enzymatic antioxidant system. Enzymes such as superoxide dismutase (SOD), the catalase and glutathione peroxidase degrades the excess ROS. Non-enzymatic scavengers such as vit E, Ubiquinone or coenzyme Q, carotenoids, Vitamin C and glutathione also detoxifies free radicals.[8] This is useful in balancing the intracellular ROS concentration within the physiological range.

As signal molecules, ROS are sensed, transmitted and converted by neurons into intracellular responses including synaptic plasticity. Mitochondrial generation of ROS occurs in the brain like in the hypothalamus. Areas of the hypothalamus like the arcuate nucleus (ARC), Ventro Medial Nucleus (VMN) and paraventricular nucleus (PVN) have shown to also express NADPH oxidases (NOX) subunits.[9]

Today, we know that hypothalamus is the flashpoint, where the process of regulating glucose homeostasis takes place. Neurons in the hypothalamus are sensitive to glucose and other nutrients. Neurons that are excited by rising glucose level are called the glucose-excited neurons or GE neurons and the neurons that are inhibited by a rising glucose level are called the glucose- inhibited neurons or GI neurons. The hypothalamus nuclei such as arcuate nucleus, POMC are considered as GE whereas the AgRP/NPY neurons are considered as GI neurons.[10] The activation of these neurons and the determination of feeding behavior are through a mechanism that is dependent on hypothalamic ROS production.

EFFECT OF NUTRIENTS AND HORMONES ON HYPOTHALAMIC ROS PRODUCTION

Studies have shown, that an intracarotid injection of glucose results in the generation and the transient release of hypothalamic ROS.[10,11] To be precise and to come closer to the point, one study have indicated that POMC neurons generate significantly more ROS under normal fed chow conditions[12] than the NPY/AgRP neurons. Even during fasting, when NPY/AgRP neurons are discharging increasingly, the production of ROS in them is not significantly seen.

This observation insinuated Andrew et al. (2008)[12] to develop a hypothesis suggesting, that a decrease in basal ROS production lead to activation of NPY/AgRP neurons in negative energy balance state and the decrease level of ROS in POMC renders these neurons silent. Activation of NPY/AgRP neurons lead to an increased food intake. In positive energy balance state, the opposite occurs in POMC neurons, the level of mROS increases resulting in the activation of POMC neurons, causing satiety and inhibition of food intake.[12]

Besides the differential response to substrate levels by the POMC and NPY/AgRP neurons, the two variants of neurons also differ in the substrate utilization for fuel. The POMC neurons apparently uses glucose as their primary fuel[13] whereas NPY/AgRP neurons are inhibited by high concentration of glucose and thrive on free fatty acids as substrate for fuel.[12,14] This has resulted in the operation of completely different mechanisms of oxidation and energy generation, with glycolysis occurring in POMC neurons and β oxidation in NPY/AgRP. Though the processes are different yet both produces ROS. However, the capacity for production of ROS by the NPY/AgRP is reported to be low.[15]

The generation of hypothalamic ROS is not only driven by nutrient sensing alone, it is also regulated by hormones like ghrelin, leptin and insulin. Ghrelin is a gut derived hormone that activates NPY/AgRP neurons and increases food intake by modulating ROS levels.[12,16,17] Leptin which is a hormone derived from adipose tissue, seems to induce increase ROS levels in POMC neurons causing a decrease in food intake and an increase in the energy expenditure.[17] Insulin also inhibits food intake by triggering the generation of hypothalamic ROS. An exception in the case of Insulin is that, the ROS level and feeding behavior is dependent on the nutritional state.[18]

FACTORS INFLUENCING GENERATION OF HYPOTHALAMIC ROS

Signals like nutrients and hormones, modulate the activity of these hypothalamic neurons in the generation of hypothalamic ROS by principally acting on the mitochondria. There is change in the mitochondrial respiration, density, number and morphology (size) that is associated with the changes in the metabolic state of these neurons.[19,20] A condition like food deprivation of 24 hours lead to an increase in mitochondria density and a decrease in the size of the mitochondria in AgRP neurons. A different picture is seen in the POMC neurons where the mitochondrial density decreases. In positive energy balance conditions like High Fat-Diet (HFD) feeding, the AgRP neurons show decrease mitochondrial density.[10,19] Changes occurring in the morphology, density and number of the mitochondria results from the processes of mitochondrial fission and fusion.

The machinery that is involved in the fragmentation or fission of mitochondria is the Dynamic Related Protein-1 (DRP 1), which is residentially cytoplasmic under basal condition. An intracarotid glucose bolus injection results in the migration of DRP 1 from the cytosol to the mitochondrial membrane increasing the level of DRP 1 in the mitochondria of VMH extract. Translocated DRP 1, forms contractile ‘ring’ on the mitochondrial membrane and facilitates mitochondrial division thereby changing the morphology and increasing the number and density of mitochondria in these hypothalamic neurons. The fragmentation of mitochondria eventually enhanced the capacity of these neurons to increase ROS production.[21]

Studies have shown that a down regulation of DRP 1 in the VMH by RNA interference leads to a defect in glucose- induced ROS production and the subsequent physiological response.[21] Other proteins which are involved in mitochondrial fission are the dynamic like protein 1 (DCP 1) and FIS 1 (Fission protein).[20]

Refusion of mitochondria on the other hand, can alter the mitochondrial dynamics resulting in the decrease capacity to generate hypothalamic ROS. Mitochondrial fusion machinery involves proteins like mitofusion (Mfn) and optic atrophy 1 (OPA 1) which are associated with the fusion process of the outer and inner membranes respectively.[20] Mfn and OPA-1 are also proteins belonging to the dynamin GTPase family.[20]

Mitochondrial function can also be affected by uncoupling proteins (UCP) particularly UCP 2, which are located in the inner membrane of the mitochondria to facilitate the transit of proton from matrix to the inner membrane space of the mitochondria.[22] UCP 2 also allows the transport of metabolites such as aspartate, malate and oxaloacetate. UCP 2 therefore can reduce substrates of Krebs cycle, decrease the activity of the electron transport chain and this can reduce the capacity to produce ROS.[23]

UCP 2 expression on mitochondrial membrane also increase the response to intraperitoneal injection of ghrelin, a hormone that is secreted in fasted state. Increased UCP 2 expression have been reported to subsequently scavenge ROS in NPY neurons without affecting ROS production in POMC neuron.[10] According to some workers, another possible physiological role of UCP is that, it responds to overproduction of matrix superoxide and catalyzes mild uncoupling which resulted in a decreased proton motive force and a decrease superoxide production from electron transport chain.[24,25]

Coppola and his coworkers, have suggested a link between this mitochondrial protein and the nutritional status, as their findings showed increase hypothalamic mRNA and protein expression of UCP 2 in fasted state.[10,26] In the same line, Andrews et al.[12] developed a hypothesis that implicates UCP 2 for decreasing basal mitochondrial ROS (mROS) production leading to activation of NPY/AgRP neurons and also reduced concentration of mROS levels in POMC, rendering these neurons inactive in fasted state or before a meal or during any state of negative energy balance. During the state of positive energy balance, mROS concentration in POMC neurons increases.[12] NPY/AgRP neurons on the other hand do not produce considerable quantity of ROS, as these neurons appear to have low ROS production capacity and a high ROS buffering capacity.[10,15]

Another factor controlling ROS production in hypothalamic neurons is calcium (Ca^{2+}). Hernandez-Fonseca et al. (2008),[27] have investigated and suggested pathways within the cell through which Ca^{2+} increases the generation of ROS during the process of glycolysis. In their study of the role of Ca^{2+} in generation of ROS in damaged neurons induced during glycolysis inhibition in cultured hippocampal neurons, their results further reveals that calcium influx through ionotropic glutamate receptors type, called NMDA (N-methyl-D-aspartate) receptors, is involved in ROS generation and eventually neuronal damage during moderate energy depletion.[27]

A study by D. Kohno et al.,[28] demonstrated the direct activation of AMPK in NPY neurons by ghrelin resulting in increased intracellular Ca^{2+}. Another study by Yang et al.,[29] reported ghrelin activation of GHSR on NPY neurons resulting in the increased intracellular Ca^{2+} level. This increased level of intracellular Ca^{2+} activates CAMKK (Calmodulin-dependent protein Kinase Kinase)[30] which in turn stimulates AMPK pathways, generates ATP, facilitates fatty acid oxidation and results in increased ROS production.[31,32]

Increase intracellular Ca^{2+} concentration leads to increase mROS generation which also elevates the cellular oxidative stress.[33] Buffering of excessive Ca^{2+} is executed by Calcium Binding Protein (CBP) like secretagogin (Scgn), thus reducing the effect of oxidative stress on these cells. The Scgn is highly expressed in NPY/AgRP neurons but not in the POMC. This probably is also the cause of the reduced capacity of NPY/AgRP neurons to produce ROS.[34] It may be mentioned here, that there is a reciprocal interaction between Ca^{2+} signaling and ROS production. We have discussed the importance of Ca^{2+} signaling in the generation of ROS but the opposite also occur where ROS regulates cellular calcium signaling. It is a known fact, that calcium, besides its role in ROS production, is also a second messenger in numerous physiological functions such as secretion, metabolism, coagulation, contraction, gene expression, cell survival and even cell death.[35]

Buffering systems are also involved in the modulation of the generation of ROS in hypothalamic neurons. We have discussed the role of CBP like Scgn, which buffers excessive ROS in the NPY/AgRP neurons. However, even in POMC neurons high levels of ROS, as seen in positive energy balance state or during intake of high fat diet, induces proliferation of peroxisomes, the cellular organelles that breaks down long chain fatty acid and produces antioxidants like catalase for neutralization of ROS.[17] Increased peroxisome proliferating receptor (PPAr) mRNA levels as seen in diabetic induced obese (DIO) mice and in high fat diet (HFD) fed mice, leads to proliferation of peroxisomes and decrease ROS production.[17]

ROS LEVELS IN HYPOTHALAMIC NEURONS INFLUENCES FEEDING BEHAVIOR

We have seen how nutrients and hormones act on the hypothalamic neurons, especially the NPY/AgRP and POMC neurons, to stimulate the production of ROS. Also

various studies have been cited, which implicates numerous factors that can modulate ROS production in at least two neuronal populations, NPY/AgRP and POMC neurons, of the melanocortin system which controls appetite, satiety and also energy expenditure. The objective of this review is to examine the role of ROS in facilitating the expression of orexigenic and anorexigenic peptides by the neurons of the melanocortin system and therefore, highlight its role in influencing the feeding behaviour.

Now it's clear that in a state of negative energy balance, like in fasting, the ROS levels decreases in NPY/AgRP neurons as a result of UCP 2 activation and that this mediates the activation of NPY/AgRP neurons. The mROS levels also reduces in the POMC neurons making these neurons silent.[12] The increased firing rate of NPY/AgRP neurons results in the expression of orexigenic peptides, neuropeptide Y(NPY), which activates feeding related NPY receptors (Y1 and Y5) and also the release of AgRP, an endogenous antagonist of MC4R present in the downstream neuronal targets (VMH), resulting in the development of appetite and therefore increase food intake.[36]

In a state of positive energy balance, the level of ROS in POMC neurons increases, thus activating these neurons to release α MSH (α melanocyte and stimulating hormone) which is a product cleaved from its precursor, the pro-opio-melanocortin peptide. α MSH mediates activation of melanocortin 4 receptors (MC4R) located in the downstream neurons of the paraventricular nucleus (PVN) resulting in decrease food intake and increase energy expenditure.[10,37]

It may be mentioned here, that a number of studies have indicated the existence of synaptic inputs influencing the activity of these two neuronal population. A recent study showed that food deprivation increases the number of excitatory inputs on NPY/AgRP neurons, activating these neurons to stimulate intake of food.[29] Ghrelin have been implicated to increase the presynaptic signaling pathway induced directly by calcium released from intracellular stores.[29] However, other studies have described the role of ROS in enhancing glutaminergic excitatory inputs[38] in the NPY/AgRP neurons.[29] This has inspired some reviewers to conclude that ROS, through these synaptic inputs, is indirectly regulating feeding behaviour.[34] However, no references have been found that implicates ROS concentration in the inhibition of POMC neurons by inhibitory GABA ergic signaling[16] originating from NPY/AgRP neurons.

SUMMARY

From several studies already highlighted in the body of this review, results demonstrate the importance of generation of ROS as a signaling molecule that is required for hypothalamic glucose sensing and induction of neuronal responses, which will influence change in the feeding behaviour. That, decrease in ROS level stimulate NPY/AgRP neurons and that, increase ROS level drives the stimulation of POMC neurons[12] only strengthen the fact that intracellular ROS level in these neurons is involved in the regulation of food intake and eventually body weight. Uncontrolled generation of ROS in these cells can however be detrimental to these cells. Excessive production of ROS in NPY/AgRP can impair the function of these cells [10] and results in the degeneration of both the NPY/AgRP and POMC neurons as well.[12] The existence of buffering systems in both the neurons like the UCP-2 and the Scgn,a Calcium Binding Protein (CBP), in NPY/AgRP, and the peroxisomes in the POMC, neutralizes the increase in the ROS level, therefore maintains the physiological neuronal activity of these cells. Chronic overproduction of ROS can cause over-activation of sympathetic nervous system,[39] which is responsible for the cause of associated pathological disorders like hypertension, neuropathy, cardiovascular and renal dysfunction complications seen in T2D (type 2 diabetes) and obesity. Excess ROS generation is also implicated in the development of neuro-degenerative disorders like parkinsonism and alzheimers.[10,40] The discussion on the consequences of the alteration of ROS concentration on these hypothalamic neurons in pathological condition, is however not within the scope of this review. The intend of this review is only to highlight the role of intracellular ROS in changing the feeding behaviour, for which reason the discussion here remains confined to the dynamics of ROS generation in response to substrate level and their impact on the hypothalamic neurons.

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