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Review

Prostaglandins and n-3 polyunsaturated fatty acids in the regulation of the hypothalamic–pituitary axis

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ABSTRACT

The hypothalamic–pituitary (H–P) axis integrates complex physiological and environmental signals and responds to these cues by modulating the synthesis and secretion of multiple pituitary hormones to regulate peripheral tissues. Prostaglandins are a component of this regulatory system, affecting multiple hormone synthesis and secretion pathways in the H–P axis. The implications of these actions are that physiological processes or disease states that alter prostaglandin levels in the hypothalamus or pituitary can impinge on H–P axis function. Considering the role of prostaglandins in mediating inflammation, the potential for neuroinflammation to affect H–P axis function in this manner may be significant. In addition, the mitigating effects of n-3 polyunsaturated fatty acids (n-3 PUFA) on the inflammation-associated synthesis of prostaglandins and their role as substrates for pro-resolving lipid mediators may also include effects in the H–P axis. One context in which neuroinflammation may play a role is in the etiology of diet-induced obesity, which also correlates with altered pituitary hormone levels. This review will survey evidence for the actions of prostaglandins and other lipid mediators in the H–P axis, and will address the potential for obesity-associated inflammation and n-3 PUFA to impinge on these mechanisms.

1. Introduction

The pituitary gland plays a predominant role in the control of homeostasis. It responds to regulatory signals from the hypothalamus by modulating the synthesis and secretion of multiple trophic hormones that control the function of target glands and peripheral tissues. In this way, the hypothalamic–pituitary (H–P) axis integrates multiple feedback mechanisms to control a range of physiological systems. Agents that can alter hypothalamic signaling or affect the pituitary response to these signals have the potential to impinge on these systems. In recent years, the role of hypothalamic signaling in the pathophysiology of obesity has received considerable attention, and multiple studies have reported a correlation between diet-induced obesity and hypothalamic functions. These studies have focused significantly on insulin and leptin sensitivity and corresponding effects on orexigenic and anorexigenic signaling mechanisms. The interplay between neuroinflammation and aberrant hypothalamic function, specifically insulin and leptin resistance, has been identified as a mechanism that may underlie this connection, and research in this area has contributed significantly to understanding the etiology of obesity and the associated metabolic derangements [1]. The effect of n-3 polyunsaturated fatty acids (n-3 PUFA) in modulating neuroinflammation has also been a significant research focus [2] in addition to the effects of n-3 PUFA in peripheral inflammation associated with metabolic syndrome [3]. However, these studies have for the most part not addressed whether these correlations extend to the full range of hypothalamic functions, particularly in the regulation of pituitary hormone secretion in the H–P axis. Consistent with this possibility, obesity has been correlated with the dysregulation of multiple pituitary hormones. A potential candidate for a causal mechanism that could mediate a connection between obesity-associated neuroinflammation and H–P axis function is the modulation of pro-inflammatory eicosanoid levels. In particular, numerous studies have indicated that prostaglandins may be a significant modulator of H–P axis function with respect to the production of pituitary hormones, but their role in disease processes affecting the H–P axis has not been broadly addressed. In light of these observations, and the potential interplay between dietary lipids, neuroinflammation, and lipid mediator synthesis, it would be informative to review the actions of prostaglandins in the H–P axis in this context, providing a framework for future investigation of the connections between obesity and altered pituitary hormone production. Additionally, as more recently identified inflammation resolving and neuroprotective lipid mediators have been characterized, in particular those derived from n-3 PUFA,

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the role of lipid mediators in the regulation of the H–P axis may be more extensive than the established effects of classical prostaglandins.

Extensive observations over the last 40 years have indicated that prostaglandins can affect the synthesis and secretion of multiple pituitary hormones in a selective manner, acting both directly at the pituitary and through the mediation of hypothalamic control. Thus, physiological states or disease processes that alter the synthesis and levels of specific prostaglandins in the hypothalamus and pituitary have the potential to affect the regulated production of multiple pituitary hormones, which could in turn elicit significant peripheral effects. Given the role of prostaglandin synthesis in inflammation, these observations have renewed significance in light of the potential role of neuroinflammation in obesity, and the involvement of the hypothalamus in its etiology. This paper will review the actions of prostaglandins in the H–P axis and the physiological processes it regulates. In addition, the correlation between obesity and H–P axis function and the potential influence of inflammation and n-3 PUFA on the prostaglandin-mediated regulation of the H–P axis will be addressed. What emerges is a perspective for the potential role of prostaglandins in the H–P axis at the nexus of inflammation, dietary lipids, and obesity.

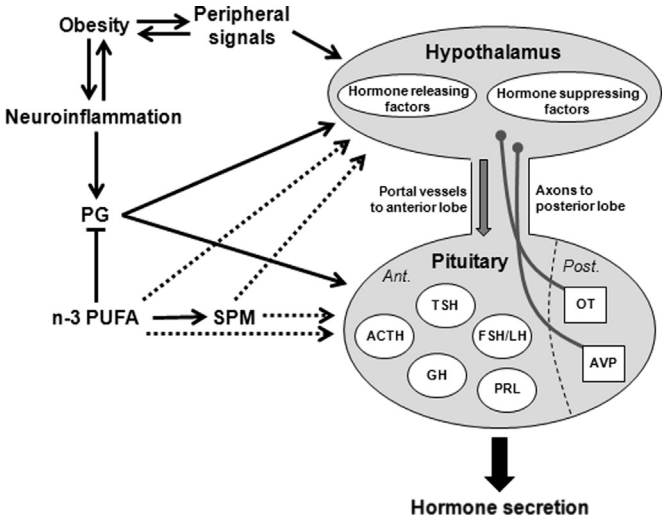

Fig. 1. Proposed model for the regulation of the H–P axis by prostaglandins and n-3 PUFA. Established functional interactions are indicated by solid arrows. Putative functional interactions are indicated by dashed arrows. Anterior pituitary (*Ant.*) cell types are indicated as white ovals and labeled with their cognate trophic hormone: ACTH, corticotropes; TSH, thyrotropes; GH, somatotropes; FSH/LH, gonadotropes; PRL, lactotropes. Posterior pituitary (*Post.*) axon termini that release oxytocin (OT) and arginine vasopressin (AVP) are indicated as white boxes. PG, prostaglandins.

2. Functional anatomy of the hypothalamic–pituitary axis

The H–P axis regulates multiple physiological processes including growth, reproduction, metabolism, and response to stress. The unitary function of the hypothalamus and pituitary reflects the coordinated ontogeny of these structures during embryonic development that results in their anatomical integration [4]. The hypothalamus receives input from both the periphery and the CNS in the form of numerous neurotransmitters, cytokines, hormones, and metabolites, and responds to these signals by the secretion of multiple hormone releasing factors or countervailing suppressors that control the synthesis and release of hormones from the anterior pituitary gland (adenohypophysis) that in turn affect peripheral tissue function. These anterior pituitary hormones include growth hormone (GH), prolactin (PRL), thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), follicle stimulating hormone (FSH), and luteinizing hormone (LH), which are synthesized by specialized cell types dispersed throughout the anterior pituitary (Fig. 1). These cell types are each operationally defined by and named for the specific peripheral target tissue of the unique trophic peptide hormone (s) that they produce. The hypothalamic parvocellular neurons that mediate anterior pituitary activity originate primarily in the paraventricular, anterior periventricular, and arcuate nuclei of the hypothalamus, which terminate in the median eminence where they secrete hormone releasing factors into the portal vasculature feeding the anterior pituitary. In addition, axon terminals from magnocellular neurons in the supraoptic and paraventricular hypothalamic nuclei extend through the median eminence and pituitary stalk into the posterior lobe of the pituitary (neurohypophysis) where oxytocin (OT) and arginine vasopressin (AVP) are stored and secreted directly into circulation (Fig. 1).

3. The diversity of lipid mediators and their precursors

Lipid mediators encompass several classes of bioactive compounds generated from precursors released from membrane phospholipids by various phospholipase A_2 (PLA_2) isoforms and other lipid-specific enzymes such as sphingomyelinase. These precursors include the n-6 PUFA arachidonic acid (AA), the n-3 PUFA DHA and EPA, lysophosphatidyl choline (LPC), and sphingomyelin, the relative levels of which vary significantly between tissues. While the primary focus of this review is the effects of classical prostaglandins on H–P axis function, largely due to the history of research in this field, prostanoids are just one class of bioactive lipid mediators that have been characterized, many of which have been observed in the brain and should also be considered in addressing the potential regulation of H–P axis function by lipid mediators going forward.

The most well-known class of lipid mediators and first to be identified are the AA-derived eicosanoids, which include the prostanoids (prostaglandins, prostacyclins and thromboxanes) generated through cyclooxygenase (COX)-dependent pathways and leukotrienes generated through lipoxygenase (LOX)-dependent pathways [5,6]. These lipid mediators regulate numerous physiological and pathological mechanisms attributable to specific eicosanoids, including but not limited to inflammation, allergy, adiposity, parturition, thrombosis, and atherosclerosis. The most pleiotropic and broadly active eicosanoid is PGE_2, which is particularly associated with inflammation [7], and in the context of this review is the predominant prostaglandin to affect H–P axis function in published findings.

A second class of lipid mediators is derived from a lysophospholipid precursor, specifically LPC, and includes platelet activating factor (PAF) and lysophosphatidic acid (LPA) [5,8]. PAF can function in several contexts such as neuropathic pain, allergy, chemotaxis, vascular permeability, and the modulation of platelet aggregation [9–12]. LPA stimulates cell proliferation involved in brain development and early embryonic growth, and is involved in processes including inflammation, neuropathic pain and lung fibrosis [13–15]. Interestingly, these pro-inflammatory mediators have also been proposed to play a role in modulating the permeability of the blood–brain barrier [16–18], which may be of significance in the context of controlling exposure of the hypothalamus to circulating agents. In addition to these LPC-derived mediators, some evidence indicates that LPC may also act directly as a lipid mediator, functioning as a ligand for several G-protein coupled receptors (GPCR) to regulate immunity [19]. An additional lysophospholipid mediator structurally similar to LPA is sphingosine-1-phosphate (S1P), which is derived from membrane sphingolipids and is involved in the regulation of vascular function and lymphocyte activity [20]. S1P has also been shown to be essential for brain development and a regulator of brain metabolism [21–23].