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Nutrition 24 (2008) 798–801

NUTRITION

www.elsevier.com/locate/nut

Central prostaglandins in food intake regulation

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Manuscript received June 3, 2008; accepted June 9, 2008.

Abstract Prostaglandin (PG) E_2 and PGD_2, produced in the mammalian central nervous system, are known to have a variety of central actions on sleep, body temperature, and pain response via G-protein–coupled seven-transmembrane receptors. We found that centrally administered PGE_2 suppressed food intake via the EP_4 receptor, whereas PGD_2 increased food intake via the DP_1 receptor coupled to the neuropeptide Y Y_1 receptor. In this review, we summarize roles of central PGs in food intake regulation and discuss the relation between PGs and neuropeptides controlling food intake.

Keywords: Food intake; Prostaglandin E_2; EP_4 receptor; Prostaglandin D_2; DP_1 receptor; Neuropeptide

Introduction

Prostaglandins (PGs), bioactive lipids produced in the central nervous system (CNS) of animals and human, are known to have a variety of central actions on sleep, body temperature, and pain response [1,2]. Among them, PGE_2 and PGD_2 are positional isomers produced from the same precursor arachidonic acid via PGH_2 and sometimes exhibit opposing biological activities in the CNS (Table 1). For example, centrally administered PGE_2 promotes wakefulness, whereas PGD_2 induces sleep [3]. PGE_2 elevates body temperature, whereas PGD_2 lowers it [4]. Recently, we found that centrally administered PGE_2 suppressed food intake via the EP_4 receptor [5], whereas PGD_2 increased food intake via the DP_1 receptor [6]. The aim of present report is to review roles of central PGs in food intake regulation and to discuss the relation between PGs and neuropeptide controlling food intake.

Anorexigenic effect of PGE_2

PGE_2 suppresses food intake via the EP_4 receptor

PGE_2, a bioactive lipid produced in the CNS of mammals, including humans, has physiologically and pathophysiologically central actions on wakefulness, fever, pain response, and food intake [3,7–10]. PGE_2 exerts its actions through four different types of G-protein-coupled seven-transmembrane receptors, known as EP_1–EP_4 [1,2]. Recently, it has been revealed that EP_3 and EP_4 mediate the febrile response and wakefulness of PGE_2, respectively [7,8]. We found that an EP_4 agonist, ONO-AE1-329, decreased food intake after intracerebroventricular administration among four highly selective EP_1–EP_4 agonists [5]. The anorexigenic action of ONO-AE1-329 and PGE_2 was blocked by an EP_4 antagonist, ONO-AE3-208 [5]. These results suggest that EP_4 activation in the CNS suppressed food intake (Fig. 1).

Hypothalamic PGE synthase and the EP_4 receptor

It is known that the hypothalamus is an important site for food intake regulation in the CNS. PGE_2 is produced from arachidonic acid by cyclo-oxygenase followed by PGE synthase and acts near its production site [1,11]. It has been reported that cyclo-oxygenase and microsomal PGE synthase are constitutively present in the paraventricular nucleus of the hypothalamus [11]. The EP_4 receptor is widely distributed throughout the entire body and its mRNA is also expressed in almost all mouse tissue. In the hypothalamus, EP_4 receptor mRNA was abundantly localized in the paraventricular nucleus and the supraoptic nucleus [12], suggesting that localization of the EP_4 receptor is partly overlapped with that of microsomal PGE synthase in the hypothalamus.

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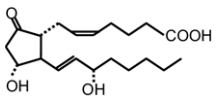
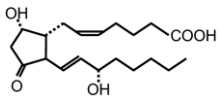
0899-9007/08/$ – see front matter
doi:10.1016/j.nut.2008.06.006

Table 1
Central actions of PGE_2 and PD_2

Action	PGE_2	PGD_2
		
Sleep	↓	↑
Body temperature	↑	↓
Food intake	↓	↑

PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2

Anorexigenic peptides activating the PGE_2–EP_4 receptor system

We investigated the anorexigenic peptides activating the PGE_2–EP_4 system, and found that angiotensins (Angs) and complement C3a agonist peptides suppress food intake via a PGE_2–EP_4-dependent mechanism [13,14]. The renin–Ang system plays an important role in the regulation of blood pressure and fluid volume, and all the components of the renin–Ang system, including angiotensinogen, enzymes responsible for releasing Angs, and Ang receptors, are present in the CNS and the peripheral endocrine system. We found that centrally administered Ang II and III suppress food intake through the Ang AT_2 receptor using an AT_2-selective antagonist and AT_2-knockout mice [13]. Furthermore, these anorexigenic activities of Ang II and III were completely blocked by an EP_4-selective antagonist [13]. Taken together, Ang II and III may suppress food intake via PGE_2 and EP_4 activation downstream of the AT_2 receptor.

Complement C3a, a polypeptide enzymatically cleaved from C3 on activation of the complement system during host defense, has a number of physiologic effects such as degranulation of mast cells, smooth muscle contraction, and increase in capillary vascular permeability. The C3a receptor is present not only in the peripheral immune system but also in the CNS including glial cells and neurons. We found that centrally administered C3a decreases food intake [15]. The anorexigenic activity of the C3a agonist peptide (Trp-Pro-Leu-Pro-Arg) was blocked by the cyclo-oxygenase inhibitor and EP_4 receptor antagonist [14]. These results suggest that the C3a agonist peptide decreases food intake through PGE_2 production followed by EP_4 activation.

Orexigenic effect of PGD_2

PGD_2 stimulates food intake via the DP_1 receptor

Prostaglandin D_2 is the most abundant PG in the mammalian CNS [16], having central actions such as sleep induction, hypothermia, and attenuation of pain response (Table 1) [3,4,17]. PGD_2 is produced by lipocalin-type PGD synthase (L-PGDS) from arachidonic acid, via PGH_2 [18]. We found for the first time that central administration of PGD_2 stimulated food intake in non-fasted mice in a dose-dependent manner [6]. Two receptor subtypes for PGD_2, DP_1 and DP_2 receptors, are G-protein-coupled receptors and present in the CNS [1,19–22]. The selective DP_1 agonist BWA245C but not DP_2 agonist 13,14-dihydro-15-keto-PGD_2 stimulated food intake after central administration at the same level as that with PGD_2 [6]. The orexigenic effect of PGD_2 was completely blocked by the selective DP_1 antagonist BWA868C [6]. Centrally administered PGD_2 did not increase food intake in mice pretreated with the DP_1-antisense oligodeoxyribonucleotide (ODN) [6]. These results suggest that the exogenous PGD_2-induced feeding is mediated by the DP_1 receptor (Fig. 1).

To investigate the role of endogenous PGD_2 in food intake regulation, we tested the effects of intracerebroventricular administration of the DP_1 antagonist or the DP-antisense ODN on food intake, body weight, and fat mass. Bolus injection of BWA868C alone significantly decreased food intake in non-fasted mice [6]. The DP_1-antisense ODN administration also markedly suppressed the daily food intake of mice in a dose-dependent manner [6]. Remarkable decreases in body weight and epididymal fat mass were also observed after administrations of the DP_1-antisense ODN [6]. Taken together, DP_1 stimulation with endogenous PGD_2 may drive the orexigenic system in the CNS that regulates food intake, body weight, and fat deposition.

Hypothalamic PGD synthase and the DP_1 receptor

The immunoreactivity of L-PGDS, responsible for the production of PGD_2 in the CNS, was present in ependymal cells facing the third ventricle and oligodendroglial cells of the median eminence of the hypothalamus [6] as well as in the leptomeninges and the choroid plexus [18,20], where PGD_2 was synthesized and secreted into cerebrospinal fluid. The DP_1-like immunoreactivity was localized in the median eminence of the hypothalamus [6]. The mRNA expression of the DP_1 was also observed in the median eminence and

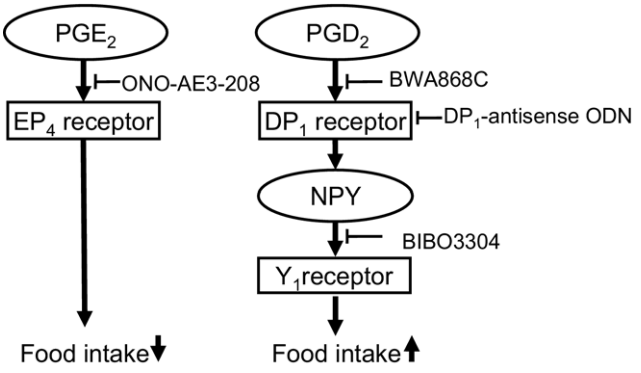


Fig. 1. Food intake regulation by central PGE_2 and PGD_2. NPY, neuropeptide Y; ODN, oligodeoxyribonucleotide; PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2.