Neuropeptide B

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Neuropeptide B (NPB) is a peptide hormone that was initially described in 2002. In humans, the biological effects of NPB depend on the activation of two G protein-coupled receptors, NPBWR1 (GPR7) and NPBWR2 (GPR8), and, in rodents, NPBWR1. NPB and its receptors are expressed in the central nervous system (CNS) and in peripheral tissues. NPB is also present in the circulation. In the CNS, NPB modulates appetite, reproduction, pain, anxiety, and emotions. In the peripheral tissues, NPB controls secretion of adrenal hormones, pancreatic beta cells, and various functions of adipose tissue. Experimental downregulation of either NPB or NPBWR1 leads to adiposity.

appetite neuropeptide B NPBWR1 NPRBWR2 metabolism energy homeostasis

1. Introduction

Peptides that regulate appetite play a prominent role in controlling energy homeostasis and whole-body metabolism. Such peptides are found in brain regions that are involved in the modulation of appetite. In addition, such peptides are present in the circulation and in numerous peripheral tissues. There is growing evidence indicating that peptides that control appetite (e.g., kisspeptin, orexins, spexin, adropin, apelin, phoenixin, ghrelin, amylin, and pancreatic peptides) also modulate the endocrine activity of endocrine glands as well as lipid and glucose metabolism [1][2][3][4][5][6]. Moreover, some peptides are involved in regulating the endocannabinoid system and, through it, food intake, e.g., hemopressin, a small peptide derived from the α-chain of hemoglobin, reduces appetite through increased levels of endocannabinoids [7][8]. On the other hand, endogenous cannabinoids can also increase the secretion of feeding-regulated hypothalamic neuropeptides [9]. Thus, peptide hormones and their receptors may be of interest in therapy for obesity and obesity-related diseases such as type 2 diabetes [1]. Almost 20 years after the discovery of neuropeptide B (NPB), there is growing evidence that this peptide modulates food intake, body weight, and lipid and glucose metabolism. In our narrative review, we discuss current findings regarding the role of NPB and its receptors in controlling food intake and energy homeostasis.

2. Discovery, Structure, and Expression of NPB and Its Receptors

By analyzing human genomic sequences in the Celera database, in 2002, Fuji et al. identified a new neuropeptide composed of 23 or 29 amino acids that was uniquely modified with bromine. This peptide was termed neuropeptide B (NPB) [10]. The same study showed that NPB interacts with NPBWR1 (GPR7) and less potently with NPBWR2 (GPR8) [10]. At the same time, NPB as a ligand of NPBWR1 and NPBWR2 was reported by two independent

laboratories [11][12]. Both NPBWR1 and NPBWR2 belong to the G protein-coupled receptor superfamily [13]. It is important to note that humans express both types of receptors, while rodents express only NPBWR1 [14]. It should be pointed out that both types of NPB receptors interact with another ligand, termed neuropeptide W [11][15]. The intracellular signaling of NPBWR1 and NPBWR1 encompasses the modulation of cAMP, calcium, phospholipase C, or MAP kinase signaling [10][11][16][17]. The expression of NPB and its receptors in the CNS and various peripheral tissues was reported (**Table 1** and **Table 2**).

Table 1. Localization of NPB in central nervous system and peripheral tissues.

	RT-PCR	ISH	IHC ICC IF	WB	NB	References
Whole brain	F	-	-	F	-	[18][19]
Telencephalic area (Vs/Vp)	-	F	F	-	F	[18][19]
Magnocellular/gigantocellular portions of magnocellular preoptic nucleus (PMm/PMg)	-	F	F	-	F	[18][19][20]
Telencephalon	Ch	-	-	-	-	[21]
Cerebral cortex	Rt	-	-	-	-	[10]
Striatum	Rt	-	-	-	-	[10]
Hippocampus	Rt, P	M, Rt	-	-	-	[10][11][22][23]
Thalamus	Rt	-	-	-	-	[10]
Hypothalamus	Rt, Ch	-	Rt	-	-	[10][21][24]
Midbrain	Rt, Ch	-	-	-	-	[10][21]
Cerebellum	Rt, P, Ch	-	Rt	-	-	[10][21][23][24]
Medulla oblongata	Rt	-	-	-	-	[10]
Spinal cord	Rt, P, Ch	-	F	-	-	[10][19][21][23]
Lateral habenular nucleus (LHb)	-	M	-	-	-	[11]
Paraventricular hypothalamic nucleus (PVN)	-	M	Rt	-	-	[11][24]
Edinger–Westphal nucleus	-	M, Rt	-	-	-	[22][24]
Motor root of trigeminal nerve (m5)	-	M	-	-	-	[11]
Sensory root of trigeminal nerve (s5)	-	M	-	-	-	[11]

	RT-PCR	ISH	IHC ICC IF	WB	NB	References
Lateral parabrachinal nucleus internal part (LPBI)	-	M	-	-	-	[11]
Mesencephalic trigeminal nucleus (Me5)	-	M	-	-	-	[11]
Subcoeruleus nucleus alpha part (Sub CA)	-	M	-	-	-	[11]
Locus coeruleus (LC)	-	M, Rt	-	-	-	[11][22]
Noradrenergic cell group A5	-	M	-	-	-	[11]
Interior olive subnucleus B (OIB)	-	M	-	-	-	[11]
Anterior olfactory nucleus	-	Rt	-	-	-	[22]
Piriform cortex	-	Rt		-	-	[22]
Supraoptic nucleus (SON)	-	-	Rt	-	-	[24]
Median preoptic nucleus	-	Rt	-	-	-	[22]
Basolateral amygdala	-	Rt	-	-	-	[22]
Medial tuberal nucleus	-	Rt	-	-	-	[22]
Substantia nigra	-	Rt	-	-	-	[22]
Dorsal raphne nucleus	-	Rt	-	-	-	[22]
Pituitary gland	Rt, Ch	-	Rt	-	-	[10][21][24]
Eyeball and optic nerve	Rt, F (eye)	-	-	-	-	[10][18]
Gill	F	-	-	-	-	[18]
Thyroid gland	Rt	-	Rt	-	-	[10][24]
Trachea	Rt	-	-	-	-	[10]
Thymus	Rt, P	-	-	-	-	[10][23]
Tonsil	P	-	-	-	-	[23]
Heart	Rt. Ch	-	Rt	Rt	-	[10][21][25]
Lung	Rt, Ch	-	-	--	-	[10][21]
Liver	Rt, Ch, F	-	-	-	-	[10][18][21]

	RT-PCR	ISH	IHC ICC IF	WB	NB	References
Spleen	Rt, Ch	-	-	-	-	[10][21]
Lymph node	Rt	-	-	-	-	[10]
Pancreas	Rt, Ch	-	Rt	-	-	[10][21][24]
Kidney	Rt, Ch	-	-	-	-	[10][21]
Adrenal gland (adrenal medulla, adrenal cortex: zonae glomerulosa and fasciculata/reticularis)	Rt	-	Rt	-	-	[10][24][26]
Urinary bladder	Rt	-	-	-	-	[10]
Peritoneum	Rt	-	-	-	-	[10]
Stomach	-	-	-	-	-	[10]
Duodenum, jejunum, ileum, cecum, colon, rectum	Rt, P, Ch	-	-	-	-	[10][21][23]
Intestine	F	-	-	-	-	[18]
Skeletal muscle	Rt, Ch	-	-	-	-	[10][21]
Prostate	Rt	-	-	-	-	[10]
Seminal vesicle	Rt	-	-	-	-	[10]
Testes	Rt, P, Ch, F	-	Rt	-	-	[10][18][21][23][24]
Ovary	Rt, P, Ch, F	-	Rt	-	-	[10][18][21][23][24]
Uterus	Rt	-	-	-	-	[10]
Placenta	Rt	-	-	-	-	[10]
Mammary gland	Rt	-	-	-	-	[10]
Skin	Rt, Ch	-	-	-	-	[10][21]
Femur	Rt	-	-	-	-	[10]
Bone marrow	Rt	-	-	-	-	[10]

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	RT-PCR	ISH	IHC ICC IF	WB	Reference
Telencephalon	Ch (R1, R2)	F (R2)	-	-	[19][21]
Cerebral cortex	Rt (R1)	-	-	-	[10]

	RT-PCR	ISH	IHC ICC IF	WB	Reference
Striatum	Rt (R1)	-	-	-	[10]
Hippocampus	Rt (R1)	M	-	-	[10]
Thalamus	Rt (R1)	F (R2)	-	-	[10][19]
Hypothalamus	Rt (R1), Ch (R1, R2)	Rt (R1), F (R2)	-	-	[10][19][21] [22][24]
Midbrain	Rt (R1), Ch (R1, R2)	F (R2)	-	-	[10][19][21]
Cerebellum	Rt (R1)	-	-	-	[10]
Medulla oblongata	Rt (R1)	-	-	-	[10]
Amygdala	-	Rt (R1)	-	-	[22]
Suprachiasmatic nucleus	-	Rt (R1)	-	-	[22]
Ventral tuberomammillary nucleus	-	Rt (R1)	-	-	[22]
Dorsal endopiriform	-	Rt (R1)	-	-	[22]
Dorsal tenia tecta	-	Rt (R1)	-	-	[22]
Bed nucleus	-	Rt (R1)	-	-	[22]
Red nucleus	-	Rt (R1)	-	-	[22]
Parastrial nucleus	-	Rt (R1)	-	-	[22]
Laterodorsal tegmentum	-	Rt (R1)	-	-	[22]
Superior colliculus	-	Rt (R1)	-	-	[22]
Locus coeruleus	-	Rt (R1)	-	-	[22]
Nucleus of solitary tract	-	Rt (R1)	-	-	[22]
Spinal cord	Rt (R1), Ch (R1, R2)	F (R2)	-	-	[10][19][21]
Pituitary gland	Rt (R1), Ch (R2)	F (R2)	-	Ch (R1, R2)	[10][19][21] [24]

	RT-PCR	ISH	IHC ICC IF	WB	Reference
Eyeball and optic nerve	Rt (R1)	-	-	-	[10]
Thyroid gland	Rt (R1)	-	-	-	[10][24]
Trachea	Rt (R1)	-	-	-	[10]
Thymus	Rt (R1)	-	-	-	[10]
Lung	Rt (R1)	-	-	-	[10]
Heart	Rt (R1)	-	Rt (R1)	Rt (R1)	[25]
Adrenal gland (adrenal medulla, adrenal cortex: zonae glomerulosa and fasciculata/reticularis)	Rt (R1)	-	-	-	[10][24][26]
Stomach	Rt (R1)	-	-	-	[10]
Duodenum, jejunum, ileum, cecum, colon, rectum	Rt (R1), Ch (R1)	-	-	-	[10][21]
Testes	Rt (R1), P (R1, R2)	-	-	-	[10][23][24]
Ovary	Rt (R1), P (R1, R2)	-	-	-	[10][23][24]
Uterus	Rt (R1)	-	-	-	[10]
Placenta	Rt (R1)	-	-	-	[10]
Mammary gland	Rt (R1)	-	-	-	[10]
Skin	Rt (R1)	-	-	-	[10]
Fetus	Rt (R1)	-	-	-	[10]
Pancreas	Ch (R2)	-	-	-	[21]
Spleen	Ch (R2)	-	-	-	[21]
Muscle	Ch (R1)	-	-	-	[21]
Brown preadipocytes	Rt (R1)	-	-	-	[11][28]
White adipocytes	Rt (R1)	-	-	-	[27]

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any influence of NPB on appetite control in animals. In contrast, i.c.v. administration of NPB during the dark phase led to stimulated food intake during the first 2 h [11]. In contrast, after 2 more hours, NPB caused appetite suppression. The same study evaluated the effects on appetite of co-administration of NPB and corticotropin-releasing factor (CRF), a well-known suppressor of food intake [18]. Tanaka et al. reported that CRF significantly

enhanced the suppression of appetite induced by NPB, suggesting an interaction between CRF and urocortin systems [11]. In summary, this study showed, for the first time, that the effects of NPB on food intake are biphasic.

The anorexigenic activity of the NPB/NPBW1 system was additionally confirmed by Ishii et al., who found that GPR7−/− male mice ate more food than wild-type GPR7 mice [19]. It is worth noting that GPR7−/− mice had reduced NPY mRNA and increased POMC mRNA expression in the hypothalamus. Of note, NPY promotes food intake, while POMC has the opposite effect [20]. Another animal study showed that i.c.v. administration of NPB (during the light phase) in male rats promoted feeding behavior [21]. Stimulation of food intake was detected 30 min after NPB administration and lasted at least 4 h. In contrast, NPB did not affect water intake [21]. It is important to note that, in contrast to NPBW1−/− mice, NPB−/− mice had a normal feeding behavior [22]. Studies addressing the role of NPB in appetite regulation are not restricted to rodents. For instance, it was found that i.p. injection of NPB stimulated mRNA expression of NPY and CCK1 in the hypothalamus of Nile tilapia *Oreochromis niloticus* [23]. Since NPY stimulates food intake and CCK1 suppresses appetite [24], it is difficult to define the role of NPB in controlling feeding behavior in tilapia, and more studies need to be conducted.

Discussing the contribution of NPB to appetite modulation, it is worth noting that a human study was conducted on circulating NPB in blood in patients with anorexia nervosa (AN). Grzelak et al. reported that patients who suffer from AN are characterized by lower levels of NPB in the circulation compared to healthy controls, suggesting the use of NPB in diagnosing AN [25]. Nevertheless, as pointed out in this work, NPB levels were evaluated in only 30 healthy controls and 46 patients with anorexia [25]; therefore, these results should be interpreted cautiously. The downregulation of circulating NPB levels in patients with anorexia was independently confirmed by a study of 30 healthy controls and 30 patients with AN [26]. Importantly, this study additionally showed that increased NPB levels are not affected by body weight normalization after hospitalization [26]. More studies are needed to elucidate the potential role of NPB in the diagnosis of AN.

In summary, animal studies have shown that i.c.v. administration of NPB during the dark phase biphasically modulates food intake. NPB promotes food intake during the first 2 h, followed by appetite suppression. In contrast, rat studies showed that NPB displays orexigenic effects during the light phase. The role of NPB in controlling feeding behavior is complex; therefore, more studies are needed.

4. The Role of NPB in Brain

Beside its role in feeding behavior, in the CNS, NPB modulates locomotion and analgesia [11]. An i.c.v. injection of NPB in rats significantly increased locomotion in an open-field test in both the bright and dark phases. On the other hand, Hirashima et al. demonstrated that i.c.v. injection of NPB in mice reduced locomotor activity during the dark period, but not during the light phase. The activity of mice was measured using an infrared activity monitor [27]. In experiments using Npb−/− mice, no significant differences in activity levels were found compared to littermate controls [22].

In the CNS, NPB impacts analgesia. Tanaka et al. reported that i.c.v. injection of NPB in rats reduced licking duration in the formalin test, which indicates an analgesic role of the peptide against chemically induced pain [11]. These effects could be conferred via NPB and NPBWR1, which are found in the periaqueductal gray matter and amygdala, areas that are also known to express opioid receptors [28]. It is worth mentioning that NPBWR1 binds non-selective opioid ligands such as β-endorphin [13]. The analgesic effect of NPB was also observed after intrathecal injection in the formalin test, and mechanical allodynia was inducible by carrageenan injection [29]. However, NPB had no effect on the level of thermal hyperalgesia induced by paw carrageenan injection in rats [29] and NPB−/− mice [22].

The pain response is tightly connected to anxiety [30]. The role of NPB in regulating anxiety has been investigated using the cued and contextual fear test and elevated plus maze test. NPBWR1−/− mice had similar behavior in the contextual fear test compared to wild-type mice [31]. However, unlike wild-type mice, NPBWR1−/− mice showed behavioral changes in social interactions [31]. The role of NPB in the context of social behavior was evaluated by Watanabe et al. [32]. They showed that genetic changes in NPWR1 (single-nucleotide polymorphism at nucleotide 404 resulted in an amino acid change, Y135F) modulated emotional responses to facial expression. The 404AT subjects were less submissive to angry faces than 404AA subjects.

There is evidence that NPB is involved in sleep/wakefulness [27]. An i.c.v. injection of NPB in mice during the dark period decreased time in the waking state and increased time in slow-wave sleep, whereas no change in paradoxical sleep time was observed. Moreover, NPBWR1+/− and NPBWR1−/− mice did not present any abnormalities compared with wild-type mice, indicating a modulatory role of NPB and NPBWR1 in the sleep/wakefulness pattern [27].

In summary, NPB plays a role in the regulation of locomotion and decreases locomotor activity during the dark phase. Moreover, during the dark period, NPB decreases the waking state time. It also plays an analgesic role in chemically induced pain and decreases social anxiety.

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