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Review

Neuropeptide Y: An Anti-Aging Player?

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Accumulating evidence suggests that neuropeptide Y (NPY) has a role in aging and lifespan determination. In this review, we critically discuss age-related changes in NPY levels in the brain, together with recent findings concerning the contribution of NPY to, and impact on, six hallmarks of aging, specifically: loss of proteostasis, stem cell exhaustion, altered intercellular communication, deregulated nutrient sensing, cellular senescence, and mitochondrial dysfunction. Understanding how NPY contributes to, and counteracts, these hallmarks of aging will open new avenues of research on limiting damage related to aging.

Trends

Neuropeptide Y (NPY) is associated with the aging process: transgenic rats overexpressing NPY live longer, while NPY Y_2-receptor knockout (KO) mice show a decline in cognitive function.

NPY is critical for the beneficial effects of caloric restriction: caloric restriction does not increase lifespan in NPY-KO mice.

NPY is a mediator of nutrient-sensing pathways in the hypothalamus, a brain region with a key role in the development of whole-body aging.

NPY induces autophagic flux in hypothalamic neurons, a process impaired in aging that leads to the accumulation of damaged macromolecules and organelles.

NPY contributes to the oxidant–antioxidant balance in disease models.

NPY induces angiogenesis, and the proliferation and migration of neural progenitor cells.

NPY has anti-inflammatory properties.

The Neuropeptide Y System

NPY (see Glossary) was first isolated in 1982 by Tatemoto *et al.* from pig brain [1]; together with peptide YY (PYY) and pancreatic peptide (PP), NPY is a member of the NPY, or 'PP-fold', family. Under the highest degree of phylogenetic preservation, NPY is a linear polypeptide with 36 amino acid residues, an amidated C-terminal group, and a large number of tyrosine residues [2]. It is one of the most abundant peptides in the central (CNS) and peripheral (PNS) nervous systems and other peripheral tissues [2]. The NPY receptors are the same for all members of the NPY family and belong to class A G-protein-coupled receptors (GPCR); they are called NPY Y_1, Y_2, Y_4, and Y_5 (Table 1). NPY has several physiological and pathological functions in the CNS (Table 1), such as feeding behavior, learning and memory, anxiety control, circadian rhythm, and so on [3]. Results from some studies also suggest that the NPY system is linked to the aging process. For example, transgenic rats overexpressing NPY live longer [4], while NPY Y_2-receptor knockout (KO) mice show learning deficits and memory deterioration, a decline in cognitive function that is also observed in aging [5,6]. By contrast, in animal models of aged rodents, and in brain samples from individuals with neurodegenerative disease, levels of NPY and NPY receptors are decreased in several brain areas (Table 2). Moreover, recent studies have shown that NPY is critical for the beneficial effects of **caloric restriction** on aging (Box 1). Here, we discuss and review the relevance of NPY for the hallmarks of aging proposed by López-Ótin *et al.* [7], namely: loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, **cellular senescence**, stem cell exhaustion, and altered intercellular communication.

NPY and the Hallmarks of Aging

Does NPY Change the Loss of Proteostasis Related to Aging?

Molecular chaperones are modulators of protein homeostasis, mediating protein folding and stability. Pharmacological induction of chaperones contributes to stable cellular conditions, as has been shown with heat-shock protein 72 (HSP72), which preserves muscle function and delays the progress of dystrophic pathology [8]. In the human neuroglia cell line, NPY increased the expression and release of HSP72 [9]. Both the effectiveness of this NPY-induced HSP72 effect on muscular dystrophy and its involvement with chaperone activity should be explored more fully. In addition to this chaperone activity, the **autophagy-**lysosomal system is also a proteolytic system implicated in protein quality control. Autophagy is a highly regulated process involved in the turnover of most cellular constituents, and is a critical regulator of cellular

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Table 1. General Overview of the Mammalian NPY Receptor Family[a]

NPY receptor	Agonists	Antagonists	Brain Localization	Examples of Functions in CNS	Refs
Y_1	[Leu^{31},Pro^{34}]NPY, [Leu^{31},Pro^{34}]PYY, [Pro^{34}]PYY, and [Pro^{34}]NPY	BIBP3226 and BIBO3304	Hypothalamus, cortex, hippocampus, amygdala, and thalamus	Increases appetite; anxiolytic and antidepressant effects; alcohol consumption regulation; and neuroprotection	[3,42,84–88]
Y_2	PYY-(3–36) and NPY 3–36	BIIE0246 and JNJ-5207787	Hippocampus, hypothalamus, thalamus, amygdala, brainstem, and cortex	Appetite regulation; anxiolytic antiepileptic action; neuroprotection; learning and memory; and circadian rhythm regulation	[3,5,89–93]
Y_4	PP	NA	Hypothalamus, frontal brain, hippocampus, thalamus, and amygdala	Food intake regulation; luteinizing hormone release; and neuroprotection	[3,91,94,95]
Y_5	[Ala^{31},Aib^{32}]NPY	L-152,804	Hypothalamus; thalamus, amygdale, hippocampus, and striatum	Appetite regulation; anxiolytic and anticonvulsant effects; neuroprotection; and circadian rhythm regulation	[3,91,96–98]

[a]Abbreviation: NA, not available.

Glossary

Autophagy: a highly regulated self-degradative process involved in the turnover of most cellular constituents and in the maintenance of cellular homeostasis.

Caloric restriction: a dietary regimen based on a 30–60% reduction of calorie intake without malnutrition.

Cellular senescence: irreversible arrest of cell proliferation caused by telomere shortening, nontelomeric DNA damage, impaired mitogenic and proliferation-associated signals, and activation of tumor suppressors.

Neuropeptide Y: a 36 amino acid peptide abundant in the mammalian CNS, especially in the hypothalamus, hippocampus, and nucleus accumbens. It acts as neurotransmitter or neuromodulator through GPCRs named Y_1–Y_5. NPY and NPY receptors are also present in the periphery.

homeostasis in several species [10]. Autophagy is impaired with aging, leading to the accumulation of damaged macromolecules and organelles, which contributes to the aggravation of aging and age-related diseases [11]. In the CNS, autophagy impairment contributes to neurodegeneration and the pathogenesis of neurodegenerative disorders [12]. Autophagy mediates, at least in part, the beneficial effects of caloric restriction on neurodegenerative disorders [13], and increases in lifespan [14]. Since caloric restriction increases NPY levels in the hypothalamus [15], it has recently been suggested that NPY regulates autophagy in hypothalamic neurons [16].

Box 1. NPY: A Mediator of Caloric Restriction Effects

Caloric restriction is the only nongenetic intervention that is well described to increase the average life expectancy, as well as the healthspan, of many organisms, from yeast to mammals [109]. Caloric restriction comprises a reduced caloric intake (30–60% below *ad libitum*) and protects against the deterioration of biological functions related to aging, delaying or reducing the risk of many age-related diseases [110,111]. Moreover, the major neuroendocrine effect of caloric restriction is the increase of NPY in ARC of the hypothalamus, due to its hyperphagic effect and to recover the low energy availability induced by caloric restriction [15,112]. Although it is not yet well established whether NPY is essential for the beneficial effects of caloric restriction, increases in NPY can lead to several physiological modifications similar to those induced by caloric restriction, namely the reduction of core body temperature, blood glucose levels, and fertility, and the increase in glucocorticoid secretion [15]. Ultimately, is NPY a mediator of the beneficial effects of caloric restriction? Increasing evidence demonstrates the involvement of NPY in the beneficial effects of caloric restriction: (i) NPY is implicated in the tumorigenesis repression induced by caloric restriction [36,113]; (ii) caloric restriction does not increase lifespan in NPY-KO mice [113]; (iii) in rodent hypothalamic neurons in culture, NPY receptor antagonists blocked the effects of caloric restriction on autophagy stimulation [16]; and (iv) recently, it was suggested that the thermoregulatory role of NPY could represent a potential mechanism underlying the anti-inflammatory effects of caloric restriction in the hypothalamus [114]. However, the full mechanisms underlying the role of NPY in the beneficial effects of caloric restriction are not fully known. Moreover the contribution of NPY to lifespan extension remains unexplored.