Int.J.Curr.Microbiol.App.Sci (2023) *12*(05): 143-149

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 12 Number 5 (2023)**
Journal homepage: http://www.ijcmas.com

Review Article https://doi.org/10.20546/ijcmas.2023.1205.020

Pleiotropic Effects of Phoenixin on Different Physiological Systems of Animals

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Keywords

Phoenixin, Reproduction, Inflammation, Food intake, Stress, Memory

Article Info

Received:
12 April 2023
Accepted:
07 May 2023
Available Online:
10 May 2023

A B S T R A C T

It is widely acknowledged that Phoenixin (PNX) and its receptor of GPR 173 is newly identified and primarily known that PNX only acts on the reproductive system by enhancive effect on GnRH. Later it comes to know PNX enrolled the various paths of physiological functions including inflammation, food intake, stress, memory and others. Being PNX is a novel neuropeptide and highly conserved it may be greatly accompanied by different functions. Based on the proteolytic cleavage, the PNX isoforms are total of six but the biologically active forms are PNX-14 and PNX-20 and its research is limited to a few species including mouse, rat, canine, bovine, porcine and human. In addition, the basic mechanism of PNX is not clear in many functions. This review briefly concludes that need to do more research on the role of PNX on the Reproduction, Inflammation, Food intake, Stress, Memory, and other physiological functions of animals.

Introduction

Neuropeptides are playing a vital role in carrying out the physiological functions of the body. The PNX is a novel neuropeptide discovered in the year of 2013 from the exclusion and inclusion of a human genome database utilized by bioinformatics algorithms.

The PNX was found in different types of peripheral organs counting of the stomach, heart, thymus and spleen (Yosten *et al.,* 2013). The PNX expression was found in different regions of brain including central amygdaloid nucleus(CeN), spinal trigeminal tract of medulla(sp5), spinocerebellar tract,area postrema (AP), dorsal motor nucleus (DMN), bed nucleus of the stria terminalis (BST) and mainly medial division of nucleus of the solitary tract (mNTS), in addition the duodenum, jejunum and ileum parts of the digestive tract (Prinz *et al.,* 2017). The different kinds of PNX are available including -14, -17, -20, -26, -36, -42 but the biologically active forms are only PNX-14 and -20. The original source of PNX is the small integral membrane protein 20 (Smim20) also called the C4orf52 gene (Billert *et al.,* 2020).

The PNX was found in humans, porcine, canine, bovine and fugu. The PNX is a highly conserved neuropeptide in multiple species and between the position of 20 to 45 sequences of amino acid only a single base difference was observed in humans and rodent (Yosten *et al.,* 2013). The knockdown of siRNA targeting *GPR173* is revealed that downregulation of mRNA in the arcuate nucleus and positive correlation was observed decreased LH with *GPR173*mRNA levels conformed that. After 3 years of identification of PNX its receptor (GPR173) was found (Stein *et al.*, 2016). In the last 9 years, the vital role of PNX was identified in different physiological functions like reproduction, cardiovascular system, food intake, inflammation, memory and stress etc.

Reproductive system

The PNX is a newly discovered neuropeptide that mainly acts on the central nerves system and reproduction. It affects oocyte maturation and enhances the production of a greater number of ovulated oocytes with the co-action of LH secretion (Billert *et al.,* 2020). The LH receptor expression in the testis and FSH receptor expression in ovaries are increased by PNX (Rajeswari and Unniappan, 2020). The intracerebroventricular injection of PNX in a dose-dependent manner increased LH secretion in dioestrus rats and knockdown of GPR173 is associated with the prevention of PNX–LH secretion leads to the delay of oestrous cycle (Stein *et al.,* 2016). Bisphenol A(BPA) is a ubiquitous endocrine-disrupting chemical related to reproduction functions. High-doseBPA-administered treated rats showed that the PNX gene was expressed high and significantly associated with disrupting the LH surge (Lopez-Rodriguez *et al.,* 2019). The PNX-treated model of cells expressed the GnRH and Kisspeptin (Kp) neurons in the hypothalamus. The knockdown of siRNA (GPR173) leads to the down-regulation of GnRH, GnRH receptor and Kp. It also regulates the reproductive system through GPR173 and cAMP-PKA-dependent pathway (Treen *et al.,* 2016). The developmental stages of follicular granulosa cells are expressed the PNX and its receptor of GPR173 except for the primordial stage and follicular development-related genes are positively expressed with the development of follicles in the presence of PNX and its expressed in the ovary (Xuan Phuoc *et al.,* 2019). The RNA sequence revealed that the PNX effect on 17- hydroxyprogesterone mRNA expression is positively correlated with the oocyte maturation and negatively correlate with the follistatin and bone morphogenic protein 15 mRNA expression in green-spotted puffer (Timothy *et al.,* 2022). PNX neurons are expressed in the hypothalamic supraoptic and paraventricular nuclei. The PNX can balance both effects of reproduction by enhancing the secretion of LH and non-reproductive functions like control of vasopressin and oxytocin. The intracerebroventricular injection of PNX increased the vasopressin and decreased the oxytocin of serum in rats. (Gasparini *et al.,* 2018). Polycysticovary syndrome (PCOS) is mainlya neuroendocrine disorder encompassing a number of reasons. A higher level of PNX concentration was observed in PCOS patients compared to non-PCOS patients and this disorder highly positively correlated with the higher concentration of LH in serum (Ullah *et al.,* 2017). The PCOS rats of PNX expression in the ovaries is significantly correlated with the production of LH, T and negative correlation with E2. The immunohistochemical studies indicated that PCOS rats GC cells expressed a higher level of PNX-14 (Kalamon *et al.,* 2020). GnRH secretion in the hypothalamus is not only associated with Kp and is also correlated with the PNX neuropeptide and one of the key factors that regulate PCOS in females (Szeliga *et al.,* 2022).

Inflammation

The GPR173 expression is a key factor in dental pulp inflammation but its expression is reduced conformed by Lipopolysaccharide (LPS) treatment in the presence of PNX-20. The pro-inflammatory cytokines (IL-6 and MCP-1) and adhesion molecules (VCAM-1 and ICAM-1) of mRNA expression are suppressed dose-wise of PNX. TLR-4 and MyD88 mRNA expression enhance the LPS-induced expression in inflammation but PNX-20

downregulates the expression and silencing of GPR173 leads to the suppressive effect on PNX-20 (Sun *et al.,* 2020). The pro-inflammatory cytokines are TNF-α, IL-**1**β and IL-6 expression and TLR4 activation is inhibited by the nuclear translocation of p65 protein leads to the inactivation of the nuclear factor-κB (NF-κB) signaling pathway by the action of PNX-14. These findings clearly demonstrated that PNX -14 is played a vital role in decrease the inflammation in the ischemia/reperfusion stroke (Ma *et al.,* 2020). The effect of PNX-14 on the astrocytes of mice attenuates the neuroinflammatory disorder caused by the endoplasmic reticulum. The proinflammatory transcription factors of eIF-2α, ATF4, CHOP and GADD34mRNA expression were downregulated and reactive oxygen species (ROS)and superoxide dismutase (SOD) production is suppressed in the presence of PNX-14, along with inflammasome of IL-**1**β and IL-18 protein production is inhibited (Wang *et al.,* 2020). The PNX-14 treated mice duodenal lesions are smaller than the indomethacin-induced duodenal ulcer. The pro-inflammatory cytokines levels in serum are decreased by the effect of PNX14 and the levels of the oxidative (malondialdehyde and myeloperoxidase) and anti-oxidative (SOD and catalase activity) content are decreased and increased respectively with the effect of PNX-14 compared to indomethacin (Zandeh-Rahimi *et al.,* 2022). The injection of PNX-20 intothe brain region of cerebral artery occlusion Ischemic stroke mice enhances the expression of M2 phase anti-inflammatory microglial marker genes (FIZZ1, Arg-1, YM1, IL-10) and attenuates the inflammatory M1 phase marker genes (CD11b, CD86, iNOS, TNF-α, IL-6). The mechanism behind the M2 phase microglial is that IL-4 increase the expression of the PNX-20 receptor (GPR173) (Wang *et al.,* 2022**)**. The oxygen-glucose deprivation/reoxygenation (OGD/R) inflammation in bEnd.3 brain endothelial cells are reduced by PNX-14. The ROS and NADPH oxidase 1 expression are major causes of the OGD/R injury but PNX-14 can downregulate the oxidative stress and increase the expression of nitric oxide synthase and nitric oxide leads to a reduction in inflammation (Zhang *et al.,* 2020).

Food intake

The immunohistochemical studies identified that epithelial cells of gut and liver cells of zebra fishes expressed the PNX and its receptor. The intraperitoneal injection of PNX and 7 days of fasting tremendously reduced the food intake and decreased the PNX mRNA expression respectively. Glycolytic genes are highly expressed and gluconeogenesis genes are downregulated in the presence of PNX. ATP production is increased by PNX in the zebrafish liver cells (Rajeswari *et al.,* 2020). The mRNA expression of immortal hypothalamus neurons of PNX is increased in the presence of Palmitate, Docosahexaenoic and Oleate stipulated that a strong correlation between the PNX and diet, and hypothalamic neurons of PNX have the nutrient-sensing role in cell lines (McIlwraith *et al.,* 2018). The intracerebroventricular injection of PNX-14 in the light phase increases the intake of food all total time spent in meal, meal size, meal duration, meal rate and intermeal interval and decreases satiety and satiation. The PNX may act on the physiology of neurons related to food intake stimulated meal intake (Schalla *et al.,* 2017). The gut-brain axis of physiology is needed to deeper understand the food intake role and mechanism of the PNX. The central physiology of food intake might be PNX and its receptor is a key regulator (Schalla *et al.,* 2018; Schalla *et al.,* 2019). The administration and co-administration of PNX, Neuropeptide Y1, Y5 and corticotropin-releasing factors in the chickens increased the excessive food intake but the mechanism behind the PNX needs to be evaluated (Rajaei *et al.,* 2022). The PNX decreased serum levels are positively correlated with the Body Mass Index and Ideal Body Weight of malnourished and partial weight recovery patients clearly indicating that some unknown mechanism of PNX is regulating the food intake in the body (Artur *et al.,* 2019). PNX expression is increased during 2 to 7 days of fasting and deceased the refeeding after 3hr and the PNX treated hypothalamus and liver cells are expressed the GHRH and GH emphasized that PNX role on the feed intake but mechanism need to be identified (Wang *et al.,* 2018).

Stress

The restraint stress mice brain showed that the PNX effect cause to increase the expression of Raphe Pallidus (RPa), Dorsal Motor Nucleus (DMN) and medial part of the nucleus of the solitary tract(mNTS) cells and a positive correlation with c-Fos cells expression of CeN of medial division, supraoptic nucleus, arcuate nucleus, RPa, DMN, mNTS (Friedrich *et al.,* 2020). The circulating levels of blood contain ∼0.7 ng/ml of PNX-14 and the serum plasma PNX-14 concentrations are negatively correlated to the men obese (Hofmann *et al.,* 2017). The peripheral administration of PNX attenuates the restraint stress after 15 min and the NUCB2/nesfatin-1 peptide positively regulates the significant restraint stress in mice (Schalla *et al.,* 2020). The intracerebroventricular injection of PNX-14 into the anterior hypothalamic area leads to increased GnRH mRNA expression in the hypothalamus and plasma concentration levels. The open field and plus maze experiment confirmed that PNX-14 can induce the anxiety effect in mice and in the presence of cetrorelix (antagonist) the action of PNX-14 is reduced (Jiang *et al.*,2015a). Apart from this finding need to identify the precise mechanism of PNX on stress reduction and conclude within various species.

Memory

The GnRH and its receptors is playing a vital role in the attention of memory and the learning process (Zhang and Spergel, 2012). The cerebroventricular injection of PNX-14 grabbed the memory formation and prolonged memory retentions conformed by Object Locale Recognition and Novel Object Recognition tests. The PNX-14 injection into the hippocampus leads inactivation of the GnRH receptor of cetrorelix and improves memory power and retention, also enhances the memory impairment persuade by the amyloid-β1-42 (Aβ1-42) peptide and scopolamine (Jiang *et al.,* 2015b). The plasma PNX levels are negatively associated with immediate recall in the subjective memory complaint group and didn't have any positive effect on Alzheimer's disease. The negative correlation of plasma PNX may have a wide unknown mechanism associated with memory (Yuruyen *et al.,* 2017). The above findings are not sufficient to conclude the action of PNX on the decrease or increase of memory, much more research needs to carry out in a wide variety of species.

The PNX is a novel neuropeptide even its role is quite vast in different physiological functions including reproduction, cardiovascular system, food intake, inflammation, memory and stress etc. But still need to conduct research about PNX and its role in the physiology of mechanisms in different species because of its novel peptide. The past findings are limited to a few species only. The mechanism of different functions is still unknown and if we find a more precise mechanism of PNX then it can be used as a multigenic neuropeptide.

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How to cite this article:

Menda Rajendar, Vasim Shah, Sacchidananda Bera and Das, S. K. 2023. Pleiotropic Effects of Phoenixin on Different Physiological Systems of Animals. *Int.J.Curr.Microbiol.App.Sci.* 12(05): 143-149.
doi: https://doi.org/10.20546/ijcmas.2023.1205.020