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Evaluation of neuroendocrine status in longevity

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Abstract

It is well known that physiological changes in the neuroendocrine system may be related to the process of aging. To assess neuroendocrine status in aging humans we studied a group of 155 women including 78 extremely old women (centenarians) aged 100–115 years, 21 early elderly women aged 64–67 years, 21 postmenopausal women aged 50–60 years and 35 younger women aged 20–50 years.

Plasma NPY, leptin, glucose, insulin and lipid profiles were evaluated, and serum concentrations of pituitary, adrenal and thyroid hormones were measured.

Our data revealed several differences in the neuroendocrine and metabolic status of centenarians, compared with other age groups, including the lowest serum concentrations of leptin, insulin and T3, and the highest values for prolactin. We failed to find any significant differences in TSH and cortisol levels. On the other hand, LH and FSH levels were comparable with those in the elderly and postmenopausal groups, but they were significantly higher than in younger subjects. GH concentrations in centenarians were lower than in younger women. NPY values were highest in the elderly group and lowest in young subjects.

We conclude that the neuroendocrine status in centenarians is markedly different from that found in early elderly or young women.

Keywords: Centenarians; Aging; Leptin; NPY; Hormones

1. Introduction

The hypothalamus can integrate signals from the brain, peripheral circulatory system and gastrointestinal tract in order to regulate food intake and the expenditure of energy [55]. The arcuate nucleus (ARC) plays a major role in the integration of signals regulating appetite. One neuronal circuit inhibits food intake via expression of the neuropeptides proopiomelanocortin (POMC) and cocaine-amphetamine regulated transcript (CART), whereas another stimulates food intake via expression of neuropeptide Y (NPY) and Agouti-related peptide (AgRP), two potent orexigenic peptides [73,95]. Feeding behaviour is a result of the integration of central and peripheral neural, hormonal and neurochemical signals relating to the brain and metabolic state [11].

Morphological changes in the hypothalamic nuclei and neuropeptide neurons involved in the control of energy homeostasis and hormonal secretion in aging animals and humans, have been extensively described [12,22,67,76,77,94].

The process of aging in humans is associated with increased NPY gene expression in the medial basal hypothalamus, as a response to diminished feedback inhibition by insulin or leptin [22].

NPY, a 36-amino acid peptide, is found in the central and peripheral nervous system where it acts as a neurotransmitter. Hypothalamic NPY is produced, together with other monoamines such as noradrenalin and serotonin, by NPYergic neurons of ARC and by extrahypothalamic nuclei located in the medulla oblongata [55]. Ninety percent of the total AgRP and NPY is synthesized by ARC neurons. Activation of NPY/AgRP neurons increases feeding via stimulation of NPY receptors in the paraventricular nucleus (PVN), inhibition of the melanocortin system by ARC Y1 receptors and antagonistic melanocortin (MC_3R/MC_4R) activation by

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AgRP in the PVN [95]. NPY may also inhibit the arcuate POMC neurons via ARC NPY Y1 receptors.

Leptin, the ob gene product, secreted by adipose tissue, plays a role in energy homeostasis [96]. Leptin is transported into the brain across the blood–brain barrier where it interacts with specific receptors located on neurons containing NPY [3].

A defect in its transfer across the blood–brain barrier might explain resistance to leptin, which may lead to insulin resistance [3]. Obese subjects have been found to be resistant to the regulatory function of leptin [30,43]. In humans, plasma leptin levels correlate with BMI and the percentage of body fat [7,14].

The leptin–NPY system provides an important feedback control mechanism in regulating energy metabolism. NPY is a strong orexigenic factor and has the opposite effect on energy balance to that of leptin. Despite these properties, NPY has been shown to stimulate the production of insulin, cortisol and somatostatin. In addition, this peptide inhibits GH secretion and modulates gonadotrophin release [97,98]. NPY is also one of many important factors involved in the mechanism of insulin resistance [7].

Our previous studies have shown deregulation of leptin–NPY activities in both obesity and anorexia nervosa [4,5,7,8]. Starvation leads to a decrease in serum leptin levels and affects the neuroendocrine system by activating the hypothalamo-pituitary-adrenal axis, deregulating the GH-IGF_1 system and inhibiting thyroid and reproductive functions [1,79,83]. The metabolic changes are strongly associated with hormonal disturbances.

We have also identified the potential dysfunction of the hypothalamo-pituitary system in simple obesity [8].

Gradual changes in body composition, which are characterized by an increase in fat mass, a reduction in muscle mass, an increase in body weight and changes in leptin and insulin secretion, have been observed in aging [35,39]. Moreover, a number of hormonal changes were reported to accompany aging, including deregulation of the hypothalamo-pituitary-thyroid, -adrenal and -gonadal axes, dysfunction of the GHRH-GH-IGF1 axis and disturbed function of the pancreas [39]. A slight decrease in TSH and fT3 concentrations was found in a healthy elderly population [39,46]. A gradual decline in the activity of the GH-IGF1 axis (somatopause) was also observed during aging [2,39,72]. The altered secretion of gonadotrophins and gonadal hormones leads to menopause in women and adropause in men [39]. Moreover, a gradual decrease in the production of dehydroepiandrosterone (DHEA) without changes in corticotrophin secretion (ACTH) was found in elderly subjects of both genders [39]. This process could be called adrenopause. The biological consequences of somato-, meno-, andro- and adrenopause in aging may lead to the observed metabolic disturbances and changes in body composition [39].

Age-related changes in the hormones may modify circulating leptin and NPY concentrations during aging of humans [35].

The metabolic syndrome is directly related to increased atherogenesis and mortality from cardiovascular disease [54]. It has been estimated that 15–20% of subjects over 70 years of age suffer from this syndrome. However, healthy centenarians, compared with aged subjects, had a lower fat-free mass, preserved glucose tolerance and insulin action, a lower atherogenic plasma lipid profile and higher resting metabolic rate (RMR) [60–63,68].

The differences in the metabolic status between long-lived humans (centenarians) and aged subjects may be connected with changes in neuroendocrine regulation.

The aim of this study was to examine the neuroendocrine status of aging humans, especially the release of NPY and leptin, two peptides involved in the control of energy homeostasis and hormone secretion, and to determine the relationship between neuroendocrine and metabolic changes.

2. Materials and methods

2.1. Materials

The study population of 155 Caucasian women was divided into groups according to age:

(a) 78 extremely old women (centenarians) aged above 100 years, 100–115 years (mean 101.4 ± 2.02 years);
(b) 21 early elderly women aged 64–67 years (mean 66.10 ± 2.18 years);
(c) 35 younger women aged 20–50 years (mean 34.9 ± 8.0 years);
(d) Additionally, 21 postmenopausal women aged 50–60 years (mean 58 ± 5.0 years), 5–10 years after their last menstruation, were included to examine serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels.

The centenarians and early elderly women were randomly selected from citizens living in Poland. The postmenopausal women were recruited from outpatient clinics. The young women were volunteers. All subjects were in good health without relevant acute or chronic disorders including cardiovascular, respiratory and renal diseases. None of the subjects were receiving treatment for systemic, infectious, inflammatory or malignant disorders at the time of the investigation. Moreover, diabetic patients treated with oral therapy or insulin were not included in the study. Other exclusion criteria included endocrine diseases, neoplasm history and heart, respiratory, renal or hepatic failure. Additionally, none of the subjects had smoked for at least two years prior to the study nor had they a history of excessive alcohol consumption.

Informed consent was obtained from all the subjects or their relatives. The study protocol was approved by the Ethics Committee of the Polish Academy of Science.