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The Serotonin: A Piece of The Bone Integrity Puzzle?

Medical Science

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Mara Carsote

Assistant Professor of Endocrinology, Carol Davila University of Medicine and Pharmacy & C.I.Parhon National Institute of Endocrinology, Bucharest, Romania

ABSTRACT

The control of bone metabolism includes various molecules including a neural control. Among them serotonin has a dual behaviour. In the brain the monoamine acts as neurotransmitter and stimulates the bone formation by interacting with leptin, adiponectine, etc for the energy control and in the periphery induces bone loss. The gut derivate serotonin arrives via platelets to the bone, and its amount is controlled but serotonin trans-membrane transporters while the serotonin originating from the bone cells displays an autocrine skeleton control. The two antagonist bone effects of the 5-hydroxytriptamine are independently performed even the biochemically the molecule is the same, including signal transduction as CREB. Whether and when the bone integrity puzzle will be completely elucidated is it not known but the serotonin represents a piece in this puzzle.

Introduction

The demographic impact of osteoporosis especially in menopausal is correlated to a higher and higher number of preclinical studies targeting different molecules with various roles in the bone function. One of the most interesting aspects is related to the serotonin (5-hydroxytryptamine or 5-HT), a monoamine playing different roles in humans/animals as satiety or energy balance, and in skeleton integrity. Mainly, the molecule derives from brain and gut (the enterochromaffin cells). These two different sources are separately and independent. The central serotonin displays a bone formation effect ant its role is expressed as a neurotrasmitter while the peripheral one is related to the bone loss via osteoclasts and osteoblasts receptors but some of the main effects are related to the autocoid way of functioning. The specific underling networks are still a matter of debate.

General Data

Central serotonin

The central serotonin is connected to the hypothalamus pathways regarding the energy control necessary for bone metabolism including the continuum equilibrium between bone resorption and formation. **(1)** The skeleton remodelling requires a high quantity of energy thus the brain neural circuits control the bone via mediators as serotonin or leptin. **(2)** The central effect of leptin as an adipose tissue molecule is in relationship to the brain serotonin in order to control the food intake. It is known the negative correlation between the central monoamine and weight via food intake by targeting 2C and 1B receptors. **(3)** The intraventricular leptin injection in rats causes low brain serotonin in contrast to the high ranges of leptin suggesting that serotonin modulates leptin uptake by hypothalamus. **(4)** The cerebral serotoninergic satiety pathway involves 5-HT1B, 5-HT2C, 5-HT6 receptors located at the hypothalamus level (arcuate and paravertebral nucleus) and non-hypothalamus sites as nucleus of solitary tract. By these, serotonin interferes with the Neuropeptide Y which is an orexigenic molecule and alpha-MSH (melanocyte stimulating hormone) that has anorectic effects. **(5)** The communication with food behaviour related molecules as leptin also associates bone integrity control. Leptin may inhibit 5-HT release by connected neurons at the hypothalamus. Thus, if serotonin binds to the arcuate nuclei via HT1A and HT2B receptors has a positive control on appetite, and if it binds to ventromedial nuclei via HT2C receptors has a positive effect on bone accrual mass. **(6)** The skeleton related serotonin is produced at midline raphe nucleus. **(7)** But the central serotonin does not cross the brain-blood barrier so the serotonin from the bone has a peripheral distinct origin. It seems that the central and peripheral levels may be correlated in some circumstances as stressful situations. **(8)** Regardless the origin, the serotoninergic pathways are generally considered as part of the bone neural control. The central serotonin production is activated via the hypotahalmic tryptophan hydroxylase type 2 if adiponectin, an adipocyte biomarker also correlated to the energy homeostasis, is centrally administrated in APN-knockout mice. This is associated at the bone level with a lower number of osteoclasts and a higher trabecular bone mass. **(9)** The brain 5-HT inhibits the sympathetic system effecting the augmentation of bone formation. **(10)** Yet, there are still unknown pathways, for instance, the Tph2-deficient mouse which do not express the brain serotonin synthesis display a lean phenotype with no clear effect on bone, neither depression-like symptom. **(11)**

Peripheral serotonin

The bone neural control by peripheral serotoninergic paths has a dual origin: a distant indirect site from the gut coming to bone via blood (mainly into platelets) and a direct source from the skeleton itself. **(8)** Both osteoblasts and osteocytes have been described as having the potential of producing 5-HT by evidence of tryptophan hidroxylase (both at mRNA and protein expression). **(8)** The gut derived serotonin is controlled by tryptophan hydroxylase 1 activity which is modulated by Lrp5 (Low-density lipoproiein receptor-related molecule). **(12)** Lrp5 is located at the osteblasts membrane directly targeting the skeleton integrity via Wnt/beta-catenin pathway. **(13)** The Lrp5 deficient mouse has low 5-HT and a high bone mass phenotype confirming the negative bone control of serotonin. **(12)** Recently, it was shown that serotonin modulates components of the bone matrix as plasma fibronectin with effects on matriceal collagen. In osteoblasts cultures the exposure to serotonin impaired the formation of adequate quality collagen via fibronectin. **(14)** The type 1B serotonin receptor on osteoblast decreases its proliferation. Canine models in COS osteosarcoma cell lines and osteoblasts lines proved that the exposure to serotonin enhances the cancer cells but not normal osteoblasts and the specific blocker of the receptor namely SB224289 decreases the viability of both cells but with a higher effect in cancer line, potentially mediated via CREB and ERK signal transduction. **(15)** Even central and peripheral serotonin exhibits opposite effects on bone in a unique model between nature molecules, they both use CREB to affect the skeleton. **(16)** In rats, experimental osteoporosis was induced after chronic exposure to serotonin. **(17)** Also in rat models, the blocking of tryptophan hydroxylase 1 which is involved in peripheral serotonin synthesis with ursolic acid derivates the levels of serotonin are down in blood and intestine, and the bone mass is higher. This pathway has the potential of anabolic medication in osteoporosis. **(18)** Moreover, the serotonin pathway is involved in the muscle strength and contractility. Experiments in rats under L-Tryptophan free diet (the main source of serotonin production is the amino acid tryptophan) proved important changes of the structure and histology of the muscles. **(19)** Another important aspect is related to the way that serotonin arrives from intestinal cells to the bone cells via bloodstream. This introduces the serotonin transporter system and its gene manipulation as a potential target therapy with respect to

enhance of the bone mass, and also, because the antidepressant drugs are attached to the transporter, the total amount of available serotonin is changed, thus the potential skeleton effects**. (20)** The 5-HT transporter is the principal tool of controlling the amount of extracellular 5-HT. **(21).** It represents a membrane glycoprotein that allows the entrance of serotonin into the cells. The main uptake in blood is into thromocytes but the same but the same blood of 5-HT internalisation is found in central neurons. **(23)** As the brain – bone interaction via serotonin or leptin continues, the bone feeds back the brain via markers as ostecalcin that modulates leptin or insulin secretion. **(22)** Clinical observations in menopausal women with low bone mineral density pointed some correlations between peripheral serotonin as assayed by venous punction and bone turnover markers as osteocalcin or alkaline phosphatase. **(24)**

Conclusion

The serotonin embraces a special behaviour targeting the skeleton integrity: positive in correlation to the central neural control and negative in relationship with the periphery. The cerebral pathway is correlated to the appetite and energy control indirectly targeting the bone economy while the direct effects on bone are consecutive to the serotonin of gut origin and the local one with autocrine function.

Conflict of interest: none

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