

5-HYDROXYTRYPTAMINE AND SKELETON STATUS

MD, PhD, Assistant Professor, Mara Carsote¹, MD, PhD,
Assistant Professor, Dan Nicolae Paduraru², MD, PhD, Lecturer Adriana Elena Nica², MD, PhD,
Lecturer Ana Valea³, MD, PhD, Associate Professor Adina Ghemigian¹

¹“Carol Davila” University of Medicine and Pharmacy,

“C.I. Parhon” National Institute of Endocrinology, Bucharest

²University Emergency Hospital, “Carol Davila” University of Medicine and Pharmacy, Bucharest

³Clinical County Hospital, “Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca

ABSTRACT

Introduction. 5-hydroxytryptamin (serotonin) represents a monoamine with different functions. Central neurotransmitter is related to mood, food and energy regulation and indirect positive effects on bone mass via leptin and sympathetic system. Gut-derived 5-hydroxytryptamine directly influences the skeleton through Wnt/Lrp5/beta catenin signalling with opposite actions to the central pool.

Method. This is a mini-review regarding serotonin- related bone changes.

Results and discussions. All the bone cells have receptors for 5-hydroxytryptamine while skeleton may have an intrinsic ability to locally generate it. The monoamine displays paracrine and autocrine actions, some incompletely described. One practical point is the potential bone loss in clinical situations with serotonin excess, as seen in carcinoid syndrome. Up to this moment, non-bone metastatic neuroendocrine tumours are not listed as a cause of secondary osteoporosis. Another practical aspect is the use of circulating 5-hydroxytryptamine as bone turnover marker surrogate for assessing the future fragility fracture probability. Despite some correlations with classical bone remodelling markers, no clear cut conclusion has been established yet.

Conclusion. 5-hydroxytryptamine displays complex effects on skeleton status, whether direct, indirect or local, but there are data still unknown, thus future need to connect the dots in this particular inter-disciplinary field.

Keywords: 5-hydroxytryptamine, bone, osteoporosis

INTRODUCTION

5-hydroxytryptamin or serotonin represents a complex monoamine which is produced in brain and gut, mainly with different functions (1-3). Central production is related to neurotransmitters activities as mood, food and energy regulation (4-6). Brain serotonin is also linked to positive effects on bone mass (7-9). The other source of 5-hydroxytryptamine is gut-derived and it directly influences the skeleton having opposite skeleton actions to the central pool (10-12). That is why the circulating 5-hydroxytryptamine assays might not completely reflect what happens to the bone from the serotonin point of view (13,14).

MATERIAL AND METHOD

This is a mini-review regarding serotonin- related bone changes. Most of the cited papers are

accessed via Pub Med database of English written articles. 44 out of 50 references are from 2012 to 2016, considering the novelty of the topic.

RESULTS

Central 5-hydroxytryptamine

Mouse models and later human research indentified a remodelling pathway control coming from central mainstream and involving 5-hydroxytryptamine (15-17). The link between brain and periphery is established not by central serotonin, that does not have the ability to cross the blood-brain barrier, but through leptin and sympathetic system (15-17). Brain serotonin, as neurotransmitter, communicates with others molecules involved in food intake and energy expenditure, like fat-derived adipokines. Thus, a loop of regulation between metabolic components as obesity and type 2 diabetes also in-

Corresponding author:

Assist. Prof. Dan Nicolae Paduraru, MD, PhD, “Carol Davila” University of Medicine and Pharmacy, 37 Dionisie Lupu Street, Bucharest
E-mail: dan.paduraru.nicolae@gmail.com

cludes skeleton setup (18). A key player in this complex loop is leptin, which induces the proliferation of osteoblasts and their differentiation, blocking the cells apoptosis but controversies still exist (19). Leptin also modulates the central sympathetic inputs to peripheral bone (19-21). The bone cortex is innervated by nerve fibers (regardless myelinated or not), while other innervations come from arterial and venous small vessels of the skeleton (20). These fibers provide the neural control of the bone (20). The most described system is sympathetic, while opposite parasympathetic bone influence is less described (21). A secondary frame of leptin intervention is related to osteocalcin (22,23). Osteocalcin represents a molecule produced by the bone, serving an endocrine function of insulin sensitivity by inhibiting insulin producing pancreas cells and it also is a well known bone formation marker (22,23). Osteocalcin and leptin inhibits each other based on a dual synergism (22,23). Another element of interplay between food and energy pathways and skeleton regulation includes amylin with endocrine consequences over normal feeding process, while in vitro expresses anabolic bone actions (22-24). Murine experiments in ovariectomized rats revealed that 5-hydroxytryptamine is related to pain protection mechanisms which may be enhanced by administration of anti-osteoporotic drugs as calcitonin (through type 1 receptors of serotonin 5-HT₁ located in thalamus) (25). The negative skeleton influence caused by central 5-hydroxytryptamine is tidily related to observations from large clinical studies on Selective Serotonine Reuptake Inhibitors (SSRI), which are drugs useful in depression interfering with a larger time frame of monoamine exposure (26-28). These aspects are confirmed in rats models, while in humans treated with SSRI the risk of osteoporotic fracture risk is displayed at any age, regardless females menopausal status (29-31). Young women with anorexia nervosa which involves a highly consumptive sta-

tus associate low bone mineral density, as well as circulating serotonin and leptin while the balance between bone turnover markers is changed by increased bone resorption marker CTX and decreased bone formation marker osteocalcin (32).

Peripheral 5-hydroxytryptamine

Gut-produced 5-hydroxytryptamine is produced by tryptophan hydroxylase type 1 from tryptophan, the enzyme being located on enterochromaffin cells (33). Serotonin and its 24-hours urinary derivate 5-hydroxy-indol-acetic acid serves as classical neuroendocrine markers in different types of neuroendocrine tumors regardless entero-pancreatic or lung origin (34-36). Locally, serotonin is used for digestion and microbiome activity (37-39). From gut, 5-hydroxytryptamine goes into the platelets and then to different organs, but not into the brain (40). Intestinal 5-hydroxytryptamine uses the Wnt/Lrp/beta catenin pathways to regulate skeleton health especially processes related to bone loss, opposite to central non-circulating serotonin which actually does not get directly at skeleton site (41). All the bone cells have receptors for serotonin (42-44). Some studies indicate the intrinsic ability of skeleton to product local 5-hydroxytryptamine (43,44). However the source, the monoamine displays local mechanisms at paracrine and autocrine level, which are still incompletely known up to these days (43,44). Overall, the bone regulation is done by both circulating and central 5-hydroxytryptamine but, even they share the same biochemistry, they have antagonist effects (45).

DISCUSSIONS

One practical point directly linked to intestinal serotonin bone actions is the topic of potential bone mineral density damage in clinical situations with 5-hydroxytryptamine excess, as found in carcinoid tumors (46). Controversies in this topic exist and some studies pointed no correlation between circulating level and skeleton anomalies in non-bone metastatic neuroendocrine conditions (47). Others found a lower bone mineral density at hip level in patients with neuroendocrine neoplasia, even it is difficult to predict the associated fracture risk based on serotonin metabolites (48). Up to this moment, carcinoid syndrome – associated masses are not considered a cause of secondary osteoporosis (46-48). Another practical aspect is the use of circulating 5-hydroxytryptamine as bone turnover marker surrogate for assessing the future fragility fracture

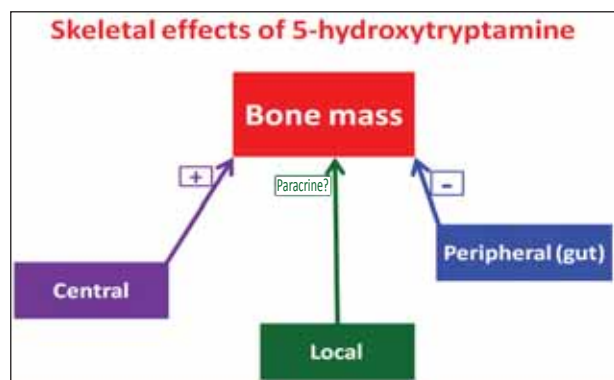


FIGURE 1. Skeletal effects of the 5-hydroxytryptamine (serotonin)

probability (49,50). Despite some correlations with classical bone remodelling markers, no clear cut conclusion has been established yet (50).

CONCLUSION

5-hydroxytryptamine displays complex effects on skeleton status, whether direct, indirect or local,

but there are still various controversial or unknown data, thus the future need to connect the dots in this particular inter-disciplinary field.

Acknowledgement: *This work has been partially supported by Carol Davila UMPH project 33878/11.11.2014/Young researchers.*

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