Seizure 48 (2017) 36–43

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The effect of VPA on bone: From clinical studies to cell cultures—The molecular mechanisms revisited

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ARTICLE INFO

Article history:
Received 7 January 2017
Received in revised form 19 March 2017
Accepted 21 March 2017
Available online xxx

Keywords:
Valproic acid
HDAC
Bone metabolism
Molecular mechanisms
Vitamin D

ABSTRACT

Purpose: Valproic acid (VPA) is a broad-spectrum antiepileptic drug, which is widely used as a first line treatment for idiopathic and symptomatic generalized epilepsy, as well as in non-epileptic psychiatric disorders in adult and pediatric patients. Although valproic acid is considered to be a generally well–tolerated drug, numerous studies have shown an increased bone loss and fracture risk in patients treated with VPA. The purpose of this review is to outline recent findings on VPA molecular mechanisms and their action on bone metabolism.
Methods: Unrestricted electronic search of medical databases, complemented by additional manual searches, was performed by August 2016.
Results/conclusion: The main effects of VPA on bone metabolism involve a decrease in osteoblast proliferation, changes in collagen synthesis as well as an induction of vitamin D catabolism. Apart from these direct actions of VPA in bone, indirect effects affecting other endocrine organs also contribute to VPA-induced bone loss.

1. Introduction

Valproic acid (2-propylpentanoic acid, *N*-dipropylacetic acid) is a branched short-chain fatty acid, which derived from valeric acid and was synthesized by Burton in 1882 [1]. Valproic acid (VPA) was initially used as molecule carrier. It was in 1963 that Meunier, while he was studying the antiepileptic effects of new molecules against seizures induced by pentelenetetrazole in experimental animals, reported that VPA prevented pentylenetetrazol-induced convulsions in rodents [2]. One year later Carraz et al. [3] carried out the first human study leading to the acknowledgement of VPA antiepileptic properties, which was approved in 1978 by FDA as a first-line anti-epileptic drug.

Despite its well-known anti-convulsive activity, VPA is also effectively used in non-epileptic conditions, such as migraine and bipolar disorders, while it has also been recently explored for its use as an adjuvant anti-cancer agent. More precisely, VPA is found to suppress tumor growth and tumor angiogenesis because of its action as histone deacetylase (HDAC) inhibitor. Histone acetylation increases gene transcription, while histone deacetylation suppresses the transcription process. VPA induces HDAC inhibition, histone acetylation and hyperacetylation accumulation, reverse HDAC-mediated transcriptional repression and subsequently mediates in various cell functions such as cell differentiation and cell apoptosis [4].

VPA is considered to be a generally well-tolerated drug with serious side effects, such as hepatotoxicity, pancreatitis and teratogenicity rarely being reported. Among its long-term side effects, osteoporosis and increased fracture risk have been extensively studied in humans presenting inconsistent results, while the underlying mechanisms remain largely unknown. In this review we outline recent studies concerning the effect of VPA on bone cells and the molecular mechanisms implicated.

2. Overview of bone metabolism

The human skeleton is composed of cortical and trabecular bone, which undergoes continuous renewal throughout lifetime. Bone remodeling occurs through highly tuned and concerted actions of the bone cells, which resorb damaged, old bone (osteoclasts) and form and lay down new bone matrix (osteoblasts)

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http://dx.doi.org/10.1016/j.seizure.2017.03.013
1059-1311/

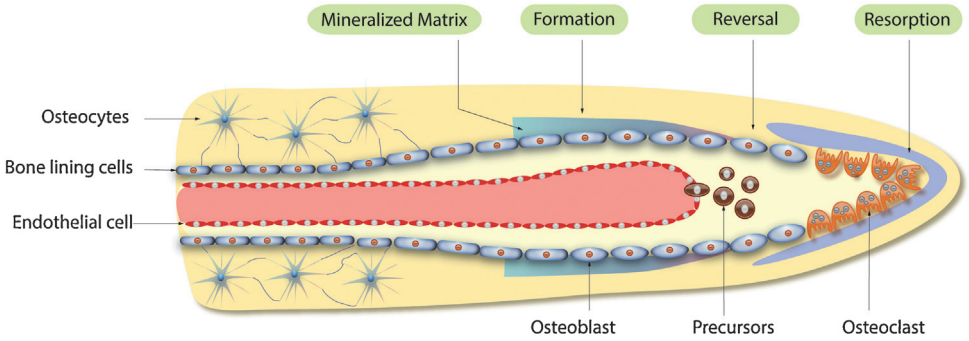

Fig. 1. A schematic overview of bone remodeling.

under the tight regulation of the osteocytes, which act as the bone mechanostat and orchestrate bone renewal according to what is needed in every bone unit (Fig. 1).

Osteoclasts are large multi-nucleated cells deriving from the mononuclear hematopoietic cell lineage. Differentiation of monocytes into active resorbing osteoclasts is regulated positively by the receptor activator of nuclear factor kappa B ligand (RANKL) and the macrophage-stimulating colony factor (M-CSF), and negatively by osteoprotegerin (OPG) [5]. Mature osteoclasts present a ruffled border, which is a series of deep folds in the area of the plasma membrane in contact with the bone matrix, secreting lysosomal enzymes, such as tartrate-resistant acid phosphatase (TRAP) and cathepsin K [6]. Bone is then resorbed by acidification and proteolysis of the collagen bone matrix and hydroxyapatite crystals [7]. During bone resorption signals secreted by osteoclasts, osteocytes or the resorbed bone matrix itself attract osteoblasts, promoting the coupling of bone resorption with bone formation.

Osteoblasts are descendants of the mesenchymal stem cell (MSC) lineage, along with adipocytes, chondrocytes, myoblasts and fibroblasts. Osteoblast differentiation from multipotent MSCs is mainly dependent on the transcription factors runt-related transcription factor 2 or osterix [8]. Bone formation takes place in three stages: 1) production of osteoid matrix, 2) maturation of osteoid matrix, and 3) mineralization of the matrix. Osteoblasts secrete various autocrine and paracrine factors, such as transforming growth factor-beta, bone morphogenetic proteins, RANKL, M-CSF and OPG [9–12]. After fulfilling their bone formation role, osteoblasts assume one of three fates: 1) undergo apoptosis, 2) remain on the bone surface as flat bone lining cells, or 3) become entombed in the newly-formed bone matrix as terminally-differentiated osteocytes. While the exact role of bone lining cells is not well understood, it has been suggested that they may be involved in the initiation of bone remodeling [13]. Osteocytes are buried in the bone matrix in lacunae, while their long slender cell

Table 1
Studies with BMD outcomes under long-term treatment with VPA.

Study	Number of participants	Age	Years of treatment	Results
Hamed et al. [38]	23	31.9 ± 5.62	10.57 ± 3.55 years	Lower BMD, BMC, Z-score, T-score at the femoral neck and lumbar spine
Triantafyllou et al. [32]	41	32.3 ± 8.2	10.6 ± 7.4	No correlation with BMD
Andress et al. [34]	31	45 ± 7	18 ± 10 years	Decrease in femoral neck BMD
Pack et al. [29]	14	30 ± 7	1 year	Unaffected
Albaghdadi et al. [33]	50	26 ± 7.2		Lower BMD and Z-score of lumbar spine and femoral neck
Serin et al. [30]	28	8.6 ± 4.6		Z-score unaffected
Sato et al. [43]	40	>18years		Decrease in BMD, T-score, Z-score of second metacarpal
Kim et al. [19]		18–50	6 months	BMD unaffected
Boluk et al. [36]		>18years	6 months	Lumbar spine, femoral neck BMD decreased
Tekgul et al. [31]	15	<18 years	2 years	Z-score unaffected
Erbayat et al. [28]		<18 years		Femoral neck BMD, lumbar spine BMD unaffected
Akin et al. [26]	25	8 years 10 months ± 6months	2.4 ± 0.2 years	L2-L4 BMD unaffected
Kumandas et al. [40]	33	8.8 ± 2		L1-L4 BMD decreased
Babayigit et al. [35]	31	11.18 ± 4.07	3.32 ± 1.09 y	BMD L1-L4 decreased
Sheth et al. [16]	13	15.4 ± 3.3	3.1 ± 1.7 y	Z-score of L2-L4, distal third of the radius decreased, reduced mineralization
Kafali et al. [39]	13	>6months	1.8 ± 0.7 y	L1-L4 BMD decreased in girls, 8% decrease in midregion of radius-ulna
Tsukahara et al. [20]	9	10.7 ± 3.3	4.6 ± 2.4y	Lumbar spine BMD decreased
Rieger-Wettengl et al. [42]	19	12.5 ± 3.7	3.7 ± 2.5	Trabecular BMD decreased
Guo et al. [21]	28	9.3 ± 0.7	>2 years	Total BMD decreased in inactive patients
Oner et al. [41]	33	7.1 ± 3.5	>6 months	Lower femoral trochanter BMD value
Song et al. [44]	92 with VPA or CBZ	<18y		Decreased BMD of mid-shaft tibia and (or) the distal third of the radius
Elliot et al. [27]	24	adults		Spine T-score and hip T-score unaffected
Gniatkowska. [37]	VPA 16, VPA + CBZ 19, VPA + LTG 32, VPA + TPM 13	7–16 years	5 years	BMD decreased

CBZ: carbamazepine, LTG: lamotrigine, TPM: topiramate, BMD: body mineral density, BMC: bone mineral content.