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GENERAL REVIEW

Interplay between bone and incretin hormones: A review

Interaction entre l'os et les hormones incrétines : une revue

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Summary Bone is a tissue with multiple functions that is built from the molecular to anatomical levels to resist and adapt to mechanical strains. Among all the factors that might control the bone organization, a role for several gut hormones called ''incretins'' has been suspected. The present review summarizes the current evidences on the effects of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) in bone physiology.

Résumé Le tissu osseux est un tissu conjonctif avec de multiples fonctions qui est organisé depuis l'échelle moléculaire jusqu'à l'échelle anatomique pour résister et s'adapter aux contraintes mécaniques. Parmi tous les facteurs qui pourraient contrôler son organisation, le rôle de certaines hormones intestinales appelées « incrétines » a émergé. La présente revue résume les connaissances actuelles sur les effets du polypeptide insulinotrope dépendant du glucose (GIP) et du glucagon-like peptide-1 (GLP-1) en physiologie osseuse.

Introduction

Bone is a tissue with multiple functions:

- it supports the body weight and protects essential organs from potential mechanical injuries (mechanical function);
- it acts as a calcium, phosphate and sodium reservoir (metabolic function);
- it is a host tissue for hematopoietic bone marrow and;
- it is also an endocrine organ involved in the regulation of glucose metabolism, energy expenditure, regulation of testosterone production and phosphate homeostasis [1—4].

From the molecular to anatomical levels, bones are built to resist and adapt to mechanical strains according to

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five different levels of organization [5]. First of all, bones have a dual composition as the bone matrix is a complex nanocomposite material made of mineral and organic phases. The organic phase is mostly composed of type I collagen (~90% of total bone proteins) and non-collagenous proteins (~10% bone proteins). The mineral phase is made of poorly crystalline hydroxyapatite tablets with hydrogen phosphate and carbonate groups substituting for phosphate ions [6]. Bone texture represents a second degree of organization. In lamellar bone, collagen is oriented in a precise way with angular changes between each lamella, giving the characteristic appearance of bone texture in polarization microscopy. Woven bone, also called non-lamellar bone, can be found in zones where osteoblast activity is very high (fracture callus, microfractures, metaplastic bone in bone metastasis, Paget's disease...) and is characterized by an anarchic texture in which collagen microfibers have random directions. Biomechanical properties of woven bone are reduced compared to those of lamellar bone. The third degree of organization is represented by the presence of osteons and arch-like bone structure units. In the cortices, the bone structural units consist of osteons with a cylindrical shape centred on a canal. Typically a complete osteon is 200–300 μm in diameter with a central canal of ~50 μm in diameter. Inside the canal, blood vessel and sympathetic nerve fibres may be observed. Canals are intercommunicating and branched to ensure the communication between periosteal and endosteal spaces. Between complete osteons are incomplete remnants of old osteons, partially eroded that constitute the interstitial bone. In trabecular bone, structural units have an arch-like appearance. These arch-like units are ~40–45 μm in thickness and represent a stack of lamellae. Trabecular bone (or cancellous bone) is sometimes improperly termed ''spongy bone''; this term is now considered as improper since it underlies a biomechanical property that bone does not have [7]. New structural units are laid over the trabecular surfaces that have been previously eroded by osteoclasts. Between the newly apposed structural units, remnants of partially eroded units persist and constitute the interstitial trabecular bone. The fourth degree is represented by the bone microarchitecture [5,7]. In the cortices, osteons are compacted so that the axes of the central canal run parallel with the resulting stress line exerted on bone. Trabecular bone tissue is composed of structural units constituting two different types of trabeculae: large plates (arranged along the stress line) connected laterally by pillars or rods, which ensure the cohesion of the network [8]. The role of trabecular bone is to resist to compression loads and transfer the strains to the cortices. Finally the fifth and last level of organization is represented by the bone macroarchitecture. Bones have special angulations and curvatures that are genetically and epigenetically determined and enable them to resist to mechanical strains, including compression, tension or shear stress loads [9,10]. As such, any modification of one of the organization level would affect the quality of the matrix, i.e. an umbrella term representing microarchitectures, microcrack propagation and tissue material properties.

To adapt to its mechanical and metabolic functions, bone is remodeled permanently by a coupling between osteoclasts, the bone-resorbing cells, and osteoblasts, the bone-forming cells responsible for the synthesis of new structural units. Osteocytes (''the third bone cell'') are derived from osteoblasts and are found embedded in the bone matrix where their main role is to serve as a mechanosensor/mechanotransducer and to inform osteoclasts and osteoblasts about bone areas that are damaged and should be remodeled. Bone remodeling is traditionally considered to be regulated by hormones (parathyroid hormone, calcitonin, estrogen...), autocrine/paracrine signals from the bone microenvironment (receptor activator of nuclear factor kappa-B ligand, tumor necrosis factor-alpha, cell-to-cell contact, etc.), mechanical loading and the central and sympathetic nervous systems.

In the quest of better understanding the different endocrine factors that may regulate bone remodeling, the role of several products from the gastrointestinal tract has been suspected. Indeed, metabolic bone disease associated with long-term parenteral feeding was first described in the early 1980s. Klein et al. reported that, in patients receiving long-term parenteral nutrition, bone physiology was altered with evidence of bone pain, hypercalciuria, elevated serum alkaline phosphatase despite normal ranges of serum calcium, phosphorus and 25-hydroxyvitamin D [11]. These findings have then been confirmed by several bone groups and are reviewed in [12]. Although these effects may be related to the composition of parenteral nutrition itself (low calcium and phosphorus, aluminum, fluoride, etc.), a role for the gastrointestinal tract can also be suspected. Further evidences are brought by a reduction in bone resorption after nutrient ingestion [13]. Indeed the elegant study of Henriksen et al. highlighted reductions of 52%, 39% and 52% after oral intake of glucose, triglycerides, and protein, respectively, in healthy individuals aged between 30 and 40 years old and with a body mass index of 22.7 kg/m^2 [13]. Furthermore, the experimental use of food fractionation results in higher bone mineral density as compared with a matched nutrient load given once a day [14].

The gastrointestinal (GI) tract is one of the largest endocrine organs with more than 12 different endocrine cells [15]. Among the plethora of bioactive peptides that the GI tract secretes, a class of peptides called incretins has emerged as important modulators of energy metabolism. The term ''incretin'' was initially proposed by Creutzfeld in 1979 and represents hormones that are secreted from the intestine in response to glucose and stimulate insulin release in a glucose-dependent manner [16]. Although several hormones with insulinotropic action are secreted by the gut, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the only two physiological incretins identified so far [17]. GIP and GLP-1 are produced by the K- and L-enteroendocrine cells, respectively, that are localized sparsely in the intestinal epithelium (Fig. 1A). Once released to the blood stream, these two hormones are rapidly degraded by an endopeptidase, the dipeptidylpeptidase-4 (DPP-4) found in the vicinity of capillaries in the intestinal mucosa or liver. DPP-4 is expressed widely as indicated in Table 1. However, due to the wide list of DPP-4 substrates, the role of DPP-4 inhibitors in bone physiology is out of the scope of this review and will not be discussed further.

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