Foreword

The idea that functional interactions exist between the nervous system and the skeleton dates at least from the 16th century. Technical advances in immunohistochemical methods a few decades ago allowed the identification of the sensory and sympathetic nerves in the periosteum and bone marrow. The types of neurotransmtters utilized and the precise nature of their interaction with bone remained undefined, however. A recent surge of interest in the role of the central nervous system and neuromediators occurred when Karsenty's group described the centrally mediated effects of leptin on bone and postulated the sympathetic nervous system as a mediator of the leptin effect. An explosion of studies since, investigating other neuropeptides and classical small molecule neurotransmitters, has produced exciting and provocative data linking the nervous system and bone biology.

In this issue of the Journal of Musculoskeletal and Neuronal Interactions, eight different articles review several neurotransmitters and their relationship to bone biology. The authors of these articles have made seminal contributions to the field. **Drs. Bonnet, Pierroz and Ferrari** describe the effects of the adrenergic nervous system on bone metabolism *in vivo* and *in vitro*, provide new evidence for a dual role of beta adrenergic receptors 1 and 2 on bone turnover, and compare the effects of beta agonists and PTH on bone. **Dr. Reid** provides a comprehensive survey of the clinical studies characterizing the effects on bone mass and the anti-fracture efficacy (or lack of it) of beta-blockers, an issue of great clinical importance given the widespread use of these drugs. **Drs. Marenzana and Chenu** summarize the evidence for involvement of β-adrenergic signaling in the response of bone cells to mechanical loading. It appears that the adrenergic nervous system may not play a direct role in load-induced bone formation, but the complexity of the interactions between the beta-adrenergic system, hormonal regulation of bone, and mechanical loading is still undefined.

A large body of data has accumulated regarding the skeletal effects of the serotonergic system. **Drs. Warden and Haney** describe the pre-clinical studies, including the conflicting nature of some of the *in vivo* findings, as well as our lack of knowledge regarding the source of serotonin acting on bone cells and the signaling pathways used. **Drs. Haney and Warden** then review the recent clinical epidemiologic studies which characterize the effects of selective antagonists of the serotonin transporter, a class of drugs known as SSRIs, on bone mass and fracture risk. The weight of the studies suggest negative effects of SSRIs on both, but issues of confounding complicate interpretation of these studies, and prospective trials are sorely needed.

No systematic review of neurobiology and bone would be complete without an update on leptin and its mediators/regulators. **Dr. Hamrick** presents some provocative new data regarding the effect of a deficiency of a proposed leptin mediator, CART, on cortical bone density, geometry and strength.

Other neuropeptides also appear to have roles in skeletal metabolism. **Dr. Lerner** reviews the evidence for effects of CGRP, substance P and VIP, including some surprising findings in mice null for the CT/α-CGRP gene and haploinsufficient for the calcitonin receptor gene. Finally, **Dr. Skerry** reviews the literature on the excitatory amino acid neuotransmitter glutamate and its role in bone turnover, discusses reasons why mechanisms like synaptic transmission are relevant to what might appear to be a slow responding tissue, and suggests the need for *in vivo* studies to complement the well-characterized *in vitro* findings.

Neuroosteology, a term first suggested to me by Ulf Lerner, has come a long way since the original description of bone innervation. This field portends not only new insights into signaling mechanisms regulating skeletal health, but also potentially unique pharmacotherapeutic agents to supplement the ones currently available.

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