

**INTESTINAL CALCIUM REGULATION
AND THE VITAMIN D₃-SYSTEM
IN TELEOSTS.**

Dennis Larsson
The University of Texas, Health Science Center at San Antonio,
Texas 78229-3900, USA
e-mail: larsson@uthscsa.edu

Björn Thrandur Björnsson¹, Ilka Nemere² and Kristina Sundell¹.
¹Fish Endocrinology Laboratory, Department of Zoology, Zoophysiology,
Göteborg University, PO-Box 463, S-405 30 Göteborg, Sweden. ²Department of
Nutrition and Food Sciences and the Biotechnology Center, Utah State
University, Logan, UT 84322-8700, USA

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The mechanisms maintaining internal calcium (Ca) homeostasis are fundamentally different between aquatic and terrestrial vertebrates. Thus, the endocrine regulation of Ca balance was probably modified during the water-to-land transition. New hormonal systems and new roles for already present hormones evolved and other hormones disappeared.

One hypothesis, suggesting that the calcium regulatory function of the vitamin D₃ system evolved simultaneously with the transition from water to land, has been put forward (Holick, 1989). However, the current knowledge about the presence and metabolism of vitamin D₃-metabolites in bony fish, together with clear roles for these metabolites in the regulation of Ca-uptake across the fish intestine, suggests an alternative hypothesis (Sundell et al., 1996). The different Ca-regulatory functions of the vitamin D₃-system seem instead to have evolved with the vertebrates, as a result of the Ca-availability in the environment.

Two major patterns of action have been revealed; one predominant in “low” calcium environments like the terrestrial and freshwater (FW) environments and a second predominant in “high” calcium environments, like the sea. The vitamin D₃-system has well documented physiological roles in intestinal Ca-regulation of both FW and seawater (SW) living teleosts. Both types of fish have the ability to metabolize vitamin D₃ to more polar metabolites, which can be measured in their circulation (Sundell et al., 1996). The classic, genome mediated increase of intestinal Ca-uptake by 1,25(OH)₂D₃, is present in all FW and SW fish examined (Sundell et al., 1996), except for the icefish *Pagothenia bernacchii* (Fenwick et al., 1994). 1,25(OH)₂D₃ induces hypercalcemia after 24 h, but not after 12 h, and classical nuclear receptors (nVDR) for 1,25(OH)₂D₃ are present in the intestine of both FW and SW species (Sundell et al., 1996). The genome mediated response seems to be vital for maintaining functional Ca-transporting mechanisms in the enterocytes, irrespective of the external Ca supply. The rapid, non-genomic actions of vitamin D₃ metabolites, on the other hand, seem to have diverged depending on the availability of Ca in the environment. Transcaltachia, the rapid increase of intestinal Ca-uptake mediated by 1,25(OH)₂D₃, has been demonstrated in terrestrial animals and FW fish (Larsson, 1999).

These two animal groups are exposed to no or very low concentrations of Ca in the environment. The marine Atlantic cod (*Gadus morhua*), on the other hand, is exposed to Ca-levels exceeding the concentrations in the blood and transcaltachia could not be demonstrated by physiologically relevant doses of 1,25(OH)₂D₃ in this species (Larsson, 1999). Plasma-membrane-bound receptors (pmVDR) for 1,25(OH)₂D₃ have also been demonstrated in FW-living fish as well as in chicken and rat, but not in the marine cod (Larsson, 1999). Instead, a second polar metabolite, 24,25(OH)₂D₃, was discovered to rapidly decrease the intestinal calcium uptake in the cod and pmVDR for 24,25 were demonstrated and biochemically characterized in this species (Larsson, 1999). However, the apparent diversion of the rapid effects of vitamin D₃ metabolites in different environments seems not fully separated, as further studies on the mechanism of action for 24,25(OH)₂D₃ demonstrate that 24,25(OH)₂D₃ rapidly decreases the intestinal Ca-uptake by inhibition of Ca-influx through L-type Ca-channels in both the marine cod and the FW-living carp (*Cyprinus carpio*) (Larsson, 1999).

Furthermore, an increase in intestinal Ca-uptake, through stimulation of Ca-influx simultaneously with a stimulation of Ca-efflux via Na/Ca-exchange, was

demonstrated in the marine cod. This effect was not exercised by $1,25(\text{OH})_2\text{D}_3$ but instead by the less polar metabolite $25(\text{OH})\text{D}_3$ (Larsson, 1999). Thus, bony fish from different environments seem to have the ability to possess both stimulatory and inhibitory rapid, non-genomic actions of the vitamin D_3 -system on intestinal Ca-uptake. However, the potency of the regulatory actions, together with number (B_{max}) and affinity (K_{m}) of pmVDR's for the different metabolites suggest that the stimulatory effect of $1,25(\text{OH})_2\text{D}_3$ is dominant in low Ca environments whereas the inhibitory effect of $24,25(\text{OH})_2\text{D}_3$ dominates in a high Ca environments. Data on a euryhaline species, the rainbow trout (*Onchoryhncus mykiss*), transferred between FW and SW supports this hypothesis. In FW, the rainbow trout possessed pmVDR for $1,25(\text{OH})_2\text{D}_3$, but not for $24,25(\text{OH})_2\text{D}_3$. After transfer from FW to SW, B_{max} and K_{m} for $24,25(\text{OH})_2\text{D}_3$ binding gradually increased to reach a steady high level after 72 h, whereas the specific binding for $1,25(\text{OH})_2\text{D}_3$ gradually decreased and was absent after 72 h. Furthermore, enterocytes from rainbow trout in FW were able to increase the Ca-influx in response to treatment with $1,25(\text{OH})_2\text{D}_3$, whereas enterocytes from trout in SW were not, and $24,25(\text{OH})_2\text{D}_3$ was able to decrease the enterocytic Ca-influx in SW- but not FW-adapted trout (Larsson, 1999).

In conclusion, available data suggest that teleosts possess antagonistic calcium regulatory systems where polar metabolites of vitamin D_3 rapidly control the amount of calcium taken up across the intestine and that the availability of calcium in the environment determines if the regulation is dominated by the stimulatory system governed by $1,25(\text{OH})_2\text{D}_3/25(\text{OH})\text{D}_3$ or the inhibitory system governed by $24,25(\text{OH})_2\text{D}_3$.

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