Vitamin D Receptor in the Paraventricular Nucleus of the Hypothalamus is Necessary for Beneficial Effects of 1,25D₃ on Peripheral Glucose Levels

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Introduction

Low vitamin D levels correlate with type 2 diabetes. However, the mechanisms by which vitamin D might regulate glucose metabolism are not well studied. The only known mechanism linking vitamin D to glucose homeostasis was identified in pre-clinical studies showing 1,25D homeostasis was identified in pre-diabetes. However, the role of vitamin D in glucose metabolism in vivo has not been explored. In the present study, we have performed studies in vivo to explore the role of vitamin D receptors in glucose metabolism.

Hypothesis

We hypothesized that central VDR activation links vitamin D to the regulation of glucose.

Methods

• For rat studies, male Long-Evans rats were placed on high fat diet (40%) for 12 weeks.
• Brain cannulations performed at least 1 week prior to studies.
• 0.1 mcg 1,25-hydroxyvitamin D₃ (1,25-OHD3) was given into the third ventricle (i3vt) or paraventricular nucleus 60 minutes prior to the studies. The vehicle was hydroxypropyl-β-cyclodextrin (THPB-EC, CTD, Inc).
• Rats with lentiviral injections had SPWGM-V463 or SPWGM-NC (Viral Vector Core, University of South Carolina) injected unilaterally into the paraventricular nucleus (PVN).
• Antagonist ZK159222 was a generous gift from Bayer Pharma AG (Berlin, Germany).
• For mice studies, VDR¹ mice were used. They received AAV9 CMV-Hil eGFP-Cre.WPRE.SV40 or AAV-CMV-GFP-9 (University of Pennsylvania Vector Core) injected bilaterally into the PVN.
• Study specific methods in the figure legends.

Results

Fig. 1. Hypothalamic 1,25D₃ lowers plasma glucose by inhibition of hepatic glucose production. A. I3vt 1,25D₃ improves glucose excursion following an i.p. bolus of dextrose in DIO rats (n = 12 vs 13). B. High-fat fed rats treated with 0.1 µg i3vt 1,25D₃ at 120 and 180 minutes during a physiologic hyperinsulinemic-euglycemic clamp had increased glucose infusion rate (n = 4-6/gp). * p<0.05 vs. vehicle.

Fig. 2. Vitamin D receptors in PVN are activated by 1,25D₃. A. VDR is present in the PVN. B. C. I3vt 1,25D₃ increases c-Fos in the PVN. This effect is diminished after pretreatment with VDR antagonist, ZK159222. * p<0.05 vs. vehicle/vehicle, # p<0.05 vs. antagonist/1,25D₃. Images 10X magnification.

Fig. 3. Vitamin D improves glucose tolerance through VDR in the PVN. A-B. Intra-PVN 1,25D₃ (0.1 µg) tends to improve glucose excursions in high-fat fed control-virus treated animals (A) but not in animals with VDR-shRNA lentivirus (B) (n = 4-6/gp). C. Intra-PVN 1,25D₃ causes a decreased in the AUC in Fig. 2A but not Fig. 2B. * p < 0.05 vs. vehicle.

Conclusions

• VDRs in the PVN are required for both exogenous and endogenous 1,25 mediated improvements in glucose regulation
• VDR activation is crucial for glucoregulation under a high-fat fed state
• Since vitamin D has limited transport into the brain, these results offer a possible explanation for the conflicting studies showing associations of vitamin D deficiency with diabetes but equivocal effects of supplementation on diabetes control.

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