Effects of vitamin D insufficiency in the fetus and in early life on vascular reactivity in young adult rats

H.C. Parkington[1], S.J. Emmett[1], R. Morley[2], C. Skordilis[1], H.A. Coleman[1] and M. Tare[1], [1]Department of Physiology, Monash University, Victoria 3800 and [2]University of Melbourne Department of Paediatrics, Royal Children's Hospital, Victoria 3052, Australia.

Inappropriate nutrition in fetal and postnatal life can lead to increased cardiovascular risk in the offspring. Vitamin D (vit D) is an important factor little studied in the context of offspring health. The prevalence of vit D insufficiency is increasing in western societies including Australia, and of particular concern, low levels are seen in pregnant women (Grover & Morley, 2001). It has been suggested that maternal vit D insufficiency may increase the risk of autoimmune disease in the offspring, with increased incidence of type 1 diabetes, chronic inflammatory disorders, some cancers, heart disease, high blood pressure, insulin resistance, and elements of Syndrome X. Here we investigated whether vit D deficiency in fetal and early life results in vasodilator dysfunction, as observed in young adult rats.

Female Sprague Dawley rats were fed chow that was vit D deficient (free of added vit D) from 4 weeks of age, with controls fed normal chow (2000U/kg cholecalciferol, vit D). This feeding regime was continued until the end of the study. After 6 weeks, all rats were mated, the litter size reduced to 10 pups on day 4 post-natal, and the pups weaned at 3 weeks of age. Pups from vit D deficient and control dams were maintained on vit D deficient and normal chow, respectively. At 7 weeks of age, a catheter was inserted into the ventral tail artery under isoflurane anaesthesia. Following 2-3 h recovery, arterial pressure was recorded for 1 h. Blood was then obtained via the catheter for serum vit D and Ca^{2+} determinations. The rats were killed by decapitation. The stage of the estrus cycle was determined from a vaginal smear, uterine weight and ovarian inspection. A segment of mesenteric artery, immediately before it entered the wall of the intestine, was mounted on a pressure myograph fitted with an in-line pressure transducer, and pressure set at 57 mmHg without flow. The segment was continuously superfused externally with bicarbonate-buffered physiological saline solution (PSS) at 35°C and 14 ml/min. Segment diameter was recorded using DIAMTRAK® (Neild, 1989). Maximal constriction was determined using 100 mM K^+ PSS and also in response to 10 μM phenylephrine. Endothelium-dependent vasodilation was tested using discrete 2 min applications of acetylcholine in the presence of 70% of maximal tone evoked with arginine vasopressin. Nitric oxide (NO) and prostanoid production was blocked as required using N^{ω}-nitro-L-arginine methyl ester (100 μM) and indomethacin (1μM), respectively.

Serum vit D levels were 8±1 ng/ml in rats fed vit D deficient chow compared with 126±10 ng/ml in controls, and serum Ca^{2+} was halved in deficient animals. Vit D deficient animals were some 20% lighter in weight than normal fed controls. Organ weights were appropriately smaller, except for the brain, in which weight was preserved in vit D deficiency. In vit D deficient rats, conscious blood pressure and heart rate were significantly greater compared with controls (by: 9±3 mmHg and 40±13 beats/min, n=11 in males; 16±4 mmHg and 24±9 beats/min, n=11 in females). Resting tone was doubled in vit D deficiency while the ability to maximally constrict was similar in all groups. Endothelium derived NO vasodilation was halved in vit D deficient males and diestrous females, while the dilation attributable to endothelium-derived hyperpolarising factor (EDHF) was preserved. Conversely, in segments from vit D deprived females in estrus, the dilation evoked by NO was preserved, while that attributed to EDHF was abolished.

These results demonstrate that vit D deprivation in fetal and early life leads to growth retardation and higher arterial pressure in young adult rats. The higher pressure was reflected in elevated resting tone in small mesenteric arteries and marked reductions in endothelium dependent vasodilation, with the vasodilators involved differing depending on the sex steroid status.

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