Possible role of the brain angiotensin system in programming and maintaining hypertension in sheep prenatally exposed to dexamethasone

A. McAlinden[1], A. Jefferies[1], M. Cock[1], E. Wintour[1], C. May[2] and M. Dodic[1], [1]Department of Physiology, Monash University, Clayton, Victoria 3800 and [2]Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, Victoria 3010, Australia. (Introduced by R. Evans)

Recent studies have generated the hypothesis that a suboptimal intrauterine environment, during a critical stage of development, 'programs' the development of fetal tissues, enabling fetal survival, but with adverse consequences in adult life (Dodic *et al.*, 2002a).

We have shown that elevated mean arterial pressure (MAP) in both male and female adult sheep can be 'programmed' by brief, prenatal exposure to an excess of the synthetic glucocorticoid (GC), dexamethasone (DEX), for only 48 hours, at day 26-28 of the 150 day gestational period (Dodic *et al.*, 1998). Late in gestation (130 days), no elevation in MAP was observed in DEX exposed fetuses, however real-time PCR studies revealed an increase in gene expression levels of angiotensinogen in the hypothalamus and angiotensin II (ANG II) type 1 (AT_1) receptors in the medulla oblongata (Dodic *et al.*, 2002b). When killed at 7 years of age, the sheep prenatally exposed to DEX were found to have increased expression of AT_1 receptors in the medulla oblongata (Dodic *et al.*, 2002b).

Our aim was two-fold: i) to determine if the brain angiotensin system (AS) contributes to the maintenance of elevated MAP; and ii) whether the sensitivity of the brain AS is altered in DEX exposed sheep. Studies were carried out on a cohort of adult male sheep prenatally exposed to either DEX (0.48mg/h) or saline (control) at 26-28 days of gestation. Sheep were instrumented with brain guide tubes (lateral ventricle) and allowed 2 weeks recovery. General anesthesia was induced with an intravenous injection of 5% Sodium Pentothal (0.4mg/kg), then the sheep was intubated and anesthesia maintained with Halothane in 100% oxygen. Cardiovascular function (MAP, cardiac output and heart rate) was measured for one hour (control period), followed by either a four hour intracerebroventricular (icv) infusion of the AT_1 receptor blocker losartan (1mg/h) or artificial cerebrospinal fluid (vehicle). In addition, brain AS sensitivity was tested by measuring cardiovascular function during icv infusions of ANG II (1 or 10μg/h), each dose running for one hour.

Our results show that the MAP response to losartan was similar between the two groups of animals. The MAP response to icv ANG II (1μg/h) was greater ($p<0.05$) in DEX exposed animals compared with the control group. The maximal MAP response to icv ANG II (1μg/h) was higher (ΔMAP=10±1.9mmHg, n=7) in the DEX group compared with the saline group (ΔMAP=6±2.1mmHg, n=7, $P<0.05$). There was no significant difference in MAP response to icv ANG II (10μg/h) between the two groups, however there was a trend towards higher maximal MAP response to ANG II (10μg/h) in the DEX group (ΔMAP=19±1.8mmHg, n=7) compared with the saline group (ΔMAP=14±2.1mmHg, n=7).

These results suggest that the basal brain AS activity does not contribute to the maintenance of elevated MAP in DEX exposed sheep. However, there might be a greater sensitivity of the brain AS to icv ANG II in the DEX exposed animals.

Dodic, M., May, C., Wintour, E. & Coghlan, J. (1998) *Clinical Science*, **94,** 149-155.

Dodic, M., Moritz, K., Koukoulas I., & Wintour, E. (2002a) *Trends in Endocrinology & Metabolism*, **13**, 403-408.

Dodic, M., Abou-Antoun, T., O'Connor, A., Wintour, E. & Moritz, K. (2002b) *Hypertension*, **40,** 729-734.