THE EFFECT OF DEHYDROEPIANDROSTERONE (DHEA) ON PENTOSE PHOSPHATE PATHWAY ACTIVITY IN RAT COLONIC TISSUE

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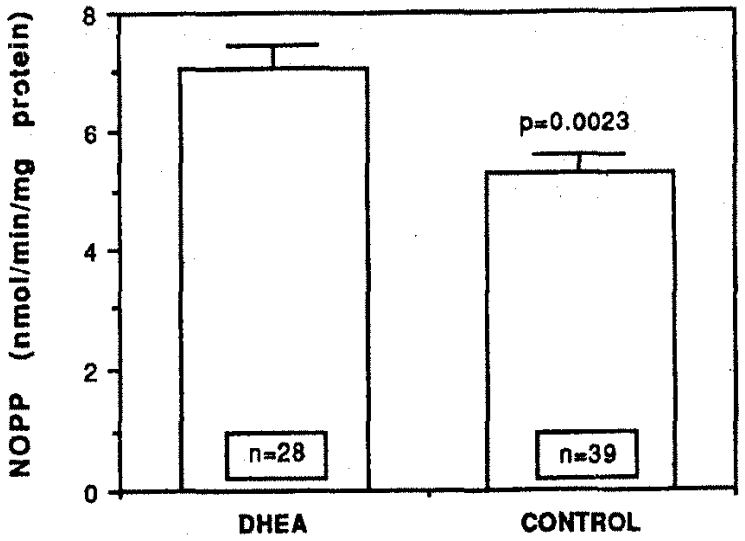
Caloric restriction is the most consistent dietary manipulation preventing tumour formation in animal models of chemically induced carcinogenesis. Preliminary evidence suggests that the metabolic and proliferative sequelae of prolonged reduced food intake show parallels with those seen when DHEA is included in the diet. In addition to inhibiting carcinogenesis DHEA diminishes cell growth *in vitro* . One hypothesis proposes that this adrenal steroid exerts its proliferative effect by inhibiting pentose phosphate production. It has been shown in a number of tissues, including the colon, the DHEA inhibits the rate limiting enzyme of the oxidative pentose pathway (OPP), glucose-6-P dehydrogenase (G-6-PDH). There is, however, an alternative pathway of metabolism for production of ribose-5-P, the non-oxidative pentose pathway (NOPP)> This study examines the effect of DHEA on the maximal catalytic activity of the NOPP in the large bowel of the rat.

Female Sprague-Dawley rats (~250 g) were injected daily with DHEA-acetate (240mg/kg i.p.) dissolved in 70% ethanol for three days. Control rats were administered an equal volume of ethanol alone. Prior to study, rats were fasted for three days and refed overnight before sacrifice at 0900 hours. Mucosal samples of caecum, proximal colon and distal colon were scraped off the underlying musculature, homogenised and centrifuged at 20,000 g for 15 minutes. The resultant cytosol was assayed for NOPP maximal catalytic activity by measuring NADPH produced during formation of hexose 6-P from ribose 5-P. Previous data from our laboratory showed that colonocyte NOPP activity in fasted/refed rats was not significantly different from that in fasted rats.



When animals which had been administered DHEA were compared with controls, a significant difference ($P<0.002$) was seen in the NOPP in pooled data from all regions of the large bowel (7.00±0.50 [DHEA] vs 5.25±0.35 [Control]nmol/min/mg protein; mean±SEM). However, when this data was stratified according to the region i.e. caecum, proximal and distal colon, only the caecum showed significantly increased NOPP activity ($P<0.01$), although the same trend was seen in all regions. We conclude that administration of DHEA results in a compensatory increase in NOPP activity, providing an alternative route of ribose 5-P production other than the OPP. Thus, the inhibitory effect of DHEA on colonic proliferation may not be due to inhibition of G-6-PDH.

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