EFFECT OF AGE AND TESTOSTERONE ON THE VASOPRESSIN RESPONSE TO DEHYDRATION IN F344BNF1 MALE RATS

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1. INTRODUCTION

Testosterone has been implicated in the dehydration-induced increase in vaspressin (VP) mRNA observed in young rats (1). Since testosterone is diminished in aged rats, and since prior studies have demonstrated a deficit in the dehydration-induced increase in VPmRNA in aged male Fischer 344 rats (2), the hypothesis that aging-associated deficits in testosterone result in a diminished VP response to dehydration was evaluated.

The VP response to dehydration was evaluated in 4, 15, and 28 mo. old male rats of the F1 cross between the Fischer 344 and Brown-Norway strains of rats (F344BNF1). This is an interesting strain for studies on the effect of aging on the VP system, because differential effects of aging have been reported in the parent strains. In male Fischer 344 rats, the plasma VP response to 72 hours of water deprivation was attenuated in 30 mo. old compared to 3 mo. old rats, and relative to body weight, VP content in the neural lobe was reduced in the older rats suggesting inadequate posterior pituitary stores of VP (3). In contrast, studies using the Brown-Norway strain reported basal activation of the hypothalamo-neurohypophyseal system in aged rats in compensation for diminished renal responsiveness to VP (4). In a previous study, 30 mo. old male F344BNF1 rats had an attenuated VP response to dehydration similar to that observed in Fischer 344 rats (5). The older F344BNF1 rats also had lower levels of testosterone compared to 4 mo. old rats. Therefore, the effect of testosterone replacement on dehydration induced stimulation of VP release, induction of VP mRNA, and renal expression of aquaporin 2 (AQP2) was evaluated.

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2. METHODS

Male F344BNF1 at 4, 15, and 28 mo. of age were obtained from the National Institute of Aging colony maintained by Harlan Sprague-Dawley. Testosterone capsules were implanted subcutaneously in half of the 28 mo old rats. All other animals received sham implants. Following 72 hrs of water deprivation or free access to water, animals were decapitated and plasma osmolality (pOsm), hematocrit (Ht), plasma VP (pVP) and testosterone concentration, posterior pituitary VP content, VP mRNA content of supraoptic nucleus (SON), and renal medullary AQP2 content was determined. VP and testosterone were measured by radioimmunoassay, VPmRNA by Northern analysis, and AQP2 by Western blot analysis.

3. RESULTS

Plasma testosterone decreased with age (ANOVA F=7.1, p=0.0035). It was significantly lower in both hydrated and dehydrated 28 mo old rats with sham implants compared to hydrated and dehydrated 15 mo old rats and hydrated 4 mo old animals. Plasma testosterone was elevated in the testosterone-treated groups compared to all other groups. Ht and pOsm were significantly and comparably increased in the water deprived groups of all ages. pVP was significantly elevated in all groups of dehydrated rats compared to their age matched control. The increase in pVP was comparable in the testosterone-treated and sham-implant 28 mo old rats. VPmRNA content of SON was increased by dehydration in the 4 mo old rats (p<0.05), but not in the 15 and 28 mo old rats. Posterior pituitary VP content was significantly decreased in the 4 and 15 mo dehydrated rats compared to their hydrated age mates, but no depletion was observed in the 28 mo old dehydrated rats. AQP2 was increased by dehydration in the 4 mo rats (p<0.05), but not in the 15 and 28 mo old animals regardless of testosterone therapy.

4. DISCUSSION

These results demonstrate that 28 mo old F344BNF1 male rats, although deficient in testosterone, are able to maintain elevated pVP over 72 hours of dehydration. This result did not replicate our previous report that pVP was not elevated following 72 hrs of dehydration in 30 mo old F1F344BN rats (5). Since the rats used in this study were 2 mos younger than in the previous study, this may suggest that deficits in the VP response reflect late-life phenomenon. In the current study, the sustained VP response in the 28 mo old rats occurred, in contrast to the young rats, independent of an increase in VPmRNA content in the SON and without depletion of posterior pituitary VP stores, suggesting that the rate of VP synthesis was adequate to meet increased synthesis demands. Thus, these results are inconsistent with the hypothesis that decreased testosterone attenuates the VP response to chronic dehydration by preventing an increase in VPmRNA.

The absence of an increase in renal AQP2 content in the dehydrated 28 mo old rats is consistent with an age related decrease in renal responsiveness to VP as previously observed in Brown-Norway rats. The failure of testosterone-treatment to correct this deficit replicates the observation that testosterone implants did not alter the elevated urinary VP excretion, polydipsia, and polyuria observed in aged Brown-Norway rats (4).