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ANTISERUM TO PROLACTIN LOWERS BLOOD PRESSURE (BP) IN SPONTANEOUSLY HYPERTENSIVE RATS

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The role of PRL in the development of hypertension in the SHR was examined by administering PRL antiserum to neonatal SHR. On days 2-7 post partum, male SHR were injected with 50 µl/day of either antiserum to PRL (which chronically lowers plasma PRL), normal rabbit serum (NRS), or 0.9% NaCl.

Heart rate, BP, and body weight were measured biweekly on weeks 6-14 of age. Anti-PRL lowered BP vs. NaCl on weeks 6, 8, 12, and 14 (range 7-17 mm Hg lower). NRS animals showed BP differences from the NaCl group only on weeks 6 and 14, with no consistent effect. Heart rates fell during the study in the NaCl and anti-PRL groups but not in the NRS group. Anti-PRL and NRS groups had higher heart rates than did the NaCl group. Body weights did not differ between groups except on week 14, when the NRS group weighed less than the NaCl group.

These results suggest that while PRL is involved in BP regulation in the SHR, it is not involved in the pathogenesis of the genetic hypertension seen in the strain. In addition, the results suggest that the serum treatment may have caused heart damage which led to an elevation in the heart rates of the serum-treated groups.

There is speculation that prolactin (PRL) may be involved in the pathogenesis of certain forms of hypertension in animals and man. This arises, in part, from reports that circulating PRL levels may be elevated in spontaneously hypertensive rats (SHR) and in humans with low renin essential hypertension, and that PRL suppression by bromocryptine lowers blood pressure (BP) in both instances (1, 2). However, interpretation of the results from PRL suppression studies is difficult, since bromocryptine raises central dopaminergic activity and may directly depress central vasomotor pathways, independent of its affect on PRL secretion (3). We have previously reported that neonatal treatment with antiserum to PRL chronically depresses basal and ether-stimulated PRL levels, as well as chronically lowering BP, in genetically normotensive male rats (4). The purpose of the current study was to examine the effects of neonatal PRL antiserum treatment on the development and maintenance of hypertension in the male SHR, independent of the hypotensive effects of dopaminergic drugs.

Materials and Methods

Six female SHR were bred prior to the study. On day 2 post partum each litter was culled to 6 pups, keeping all of the males. On days 2-7 post partum, each pup received 50 µl ip. of either 0.9% NaCl (n=6), normal rabbit serum (NRS, n=7), or antiserum to PRL (n=7). The antiserum to PRL was raised in rabbits against NIH rat PRL reference preparation RP-2. The antiserum, which was provided by Dr. S. Shin of Queen's University, bound 23 µg PRL/ml *in vitro*, and did not cross react with GH, LH, TSH, AVP, or renin at physiological concentrations (4). Subsequent to antiserum treatment, biweekly measurements of systolic BP, heart rate, and body weight were taken from age 6-14 weeks. The indirect tail cuff technique, previously described (5), was used to measure BP and heart rate in the conscious, resting animals.

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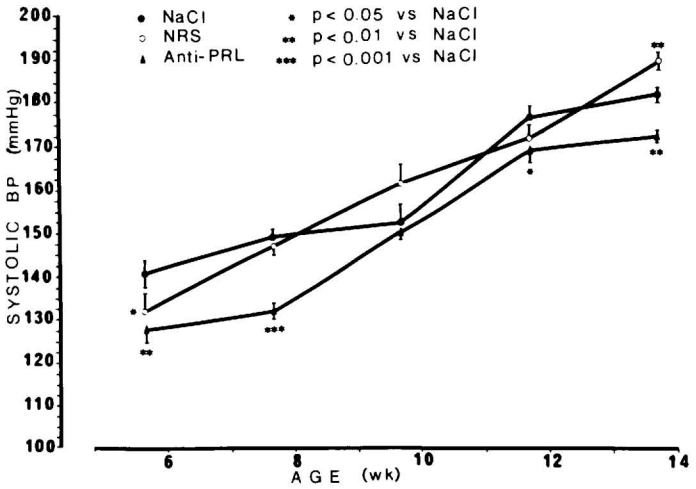

Figure 1. Systolic blood pressure (BP) of male SHR rats treated days 2-7 post partum with 0.9% NaCl (n=6), normal rabbit serum (NRS, n=7), and antiserum to PRL (n=7). ($\bar{x} \pm$ S.E.).

Data were analyzed using a 2 way ANOVA on repeated measures. Where significance of $p<0.05$ was reached, a planned comparisons test (6) was used to ascertain which points differed.

Results

The systolic BP of all 3 treatment groups rose during the 8 week study period (Fig. 1). There were no significant differences between NRS and NaCl groups except at week 6 ($p<0.05$), where the mean BP of NRS rats was less than that of NaCl rats, and week 14 ($p<0.01$), where the BP of NRS rats was greater than that of the NaCl group. In contrast, BP in the anti-PRL group was significantly lower than in the NaCl rats at week 6 ($p<0.01$), week 8 ($p<0.001$), week 12 ($p<0.05$), and week 14 ($p<0.01$).

The heart rates of all animals in the study tended to be at the upper end

Table I. Body weights and heart rates of male SHR treated on days 2-5 post partum with 50 µl of 0.9% NaCl (n=6), NRS (n=7), or antiserum to PRL (n=7). Values represent x ± S.E. *p<0.05 vs NaCl.

	Body Weight (g)			Heart Rate (min^{-1})		
	NaCl	NRS	Anti-PRL	NaCl	NRS	Anti-PRL
Week 6	92.7±1.5	83.8±4.2	96.9 ± 4.8	447±7	420±9*	429±6
Week 8	168.8±3.7	150.8±6.4	153.8±7.4	420±18	410±6	403±5
Week 10	210±2.8	213.0±6.0	210.6±9.2	383±7	411±10*	414±5*
Week 12	256.4±4.9	237.1±6.8	238.2±10.2	387±11	413±11	410±8
Week 14	276.0±4.9	250.5±6.7*	273.9±7.7	393±11	427±8*	423±9*

of the normal range (Table I). Heart rates tended to decrease from week 6-10 in the NaCl group, levelling off from weeks 10-14. Anti-PRL treated animals also demonstrated a decline in heart rate from week 6-8, but plateaued weeks 8-14 at a higher level than the NaCl group on weeks 10 and 14 ($p<0.05$). The NRS group showed no initial decline and remained at a level comparable to that of the anti-PRL group, and was significantly higher than the NaCl group on weeks 10 and 14 ($p<0.05$).

There were no differences in body weight between groups, with the exception of the NRS group which weighed less than the NaCl group on week 14 ($p<0.05$).

Discussion

It has previously been reported that PRL suppression by bromocryptine lowers systolic BP in 90-100 day old male SHR by 6 mm Hg (1). In the present study, neonatal anti-PRL treatment lowered BP in 98 day old male SHR by 11 mm Hg. This suggests that the action of bromocryptine in these animals is no greater than would be expected if its effects were mediated solely via PRL suppression, and that the modest, but significant, decline in BP reported in these animals reflects a PRL-mediated action on BP. The fact that the decrease in BP of SHR rats treated neonatally with anti-PRL was no different from that observed in genetically normotensive Sprague-Dawley rats of the same age (4), suggests that the contribution of PRL to BP is similar in the two strains of rats, and that PRL is not involved in the pathogenesis of the genetic hypertension. These findings do not however, preclude the possibility that PRL may be involved in the pathogenesis of human essential hypertension, since the SHR model is not a perfect one (7), and since there appear to be several forms of the human disorder (8). The observation in the study that NRS and anti-PRL treated animals had higher resting heart rates than did the NaCl treated animals, might result from damage to the heart caused by an immune complex disease, or serum sickness (9). The large amounts of serum could have damaged the heart tissue, necessitating higher heart rates for any given BP.

The results of the present study indicate that PRL does not contribute to the pathogenesis of hypertension in the SHR. Furthermore, they provide additional support for a role of PRL in BP regulation, possibly through modulation of vascular action of other pressor agents such as norepinephrine and angiotensin (10-12), which is independent of genetic predisposition.

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