the pentylenetetrazol, c) rats which received 10 µg of AVT 10 min before pentylenetetrazol, then 5 µg AVT at 10-min intervals starting 5 min after pentylenetetrazol (total dose 25 µg AVT). The latency to the 1st myoclonic jerk was recorded. There were 5 rats in each experimental group. Convulsions typically started with a myoclonic jerk of head and forelimbs.

Pentylenetetrazol-induced convulsions were markedly affected by AVT (fig.). Pentylenetetrazol alone caused myoclonic convulsions within a mean latency of 3.8 ± 0.4 min. Prophylactic AVT (10 µg) significantly increased the latency to convulsions to a mean of 14.8 ± 2.1 min and continued AVT treatment could further delay the convulsions to a mean of 39.3 ± 3.4 min. Indeed, when convulsions finally did occur, they were of a milder degree and shorter duration than untreated pentylenetetrazol convulsions. Rats generally laid quietly with deep breathing after AVT administration but whether this is important in protection against convulsions cannot be answered from these experiments.

Whether the AVP analog, AVT, is effective because it acts as an antagonist at the AVP receptor in the CNS, by a negative feedback mechanism on AVP in the brain or by some mechanism unrelated to AVP cannot be determined by these experiments.

The antagonistic effects of AVT on the convulsive state induced by pentylenetetrazol, suggest that the AVP analog, AVT, or other AVP analogs may be effective in the treatment of convulsive disorders.

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Spontaneously (genetic) hypertensive rats: Naloxone-reversible and propranolol-reversible decrease in pain sensitivity

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Summary. Adult spontaneously hypertensive rats (SHR) are less sensitive to painful stimuli than their normotensive controls, Wistar-Kyoto (WKY) rats. This difference can be eliminated by the specific opiate antagonist, naloxone, and by the β-adrenergic blocking agent, propranol.

Anatomical, biochemical, physiological, pharmacological and pathophysiological evidence suggests that the central regulatory mechanisms for control of pain and blood pressure are closely associated. A number of specific brain stem areas are involved in the regulation of both blood pressure and pain[2,3]. Electrical stimulation of discrete brain sites often results in coincidental changes in pain sensitivity and blood pressure[2]. Experimental evidence strongly suggests that central catecholamines are involved in blood pressure control as well as in the central regulation of pain sensitivity[2,4]. Both catecholamines and enkephalins are present in the same discrete areas involved in the integration of the central regulation of cardiovascular function[5,6]. Pharmacological manipulations of central monoamines affect the blood pressure control as well as the sensitivity to pain[7]. A decreased sensitivity to pain occurs in experimentally hypertensive rats[8].

We wish to report that spontaneously hypertensive rats (SHR)[9] are less sensitive to painful stimuli than their normotensive controls, the Wistar-Kyoto (WKY) rats, and that this difference can be eliminated by pretreatment of the animals with the specific opiate antagonist, naloxone, as well as with the β-adrenergic blocking agent, 1-propranolol.

Methods. The degree of analgesia was measured by determination of the latency time of the tail withdrawal reflex when a painful stimulus, warm water at 50 ± 1 °C, was applied to the tail of the animals (tail-flick test)[10-12]. Adult male SHR and WKY rats, 12 weeks old, were obtained from Taconic Farms (Germantown, N.Y.) and kept for 1 week under a 12-h light-dark cycle, with lights off from 18.00 to 06.00 h, before testing. Naloxone (2 mg/kg) was dissolved in saline and injected i.p. 30 min before testing. Propranolol (1 mg/kg) and clonidine (0.25 and 2.5 mg/kg) were dissolved in saline and injected i.p.; rats were tested 15 and 30 min after administration of the drugs. Control groups received saline only. Data were analyzed by a 2-way analysis of variance, and a Student Newman-Keuls test was used for comparisons of individual means[13].

Results and discussion. The SHR were significantly less responsive to the thermal stimulus than the normotensive control rats, since the latency time for the tail withdrawal reflex was increased in SHR by 145% when compared with control WKY rats (fig.).

The specific opiate antagonist naloxone produced a non-significant 28% increase in pain sensitivity of control WKY rats, but a significant, 56% increase in pain sensitivity in SHR (fig.). After naloxone treatment, hypertensive and normotensive rats no longer differed in their latency time for the tail withdrawal effect (fig.). The β-adrenergic blocking drug, 1-propanolol, produced no change in pain sensi-

tivity in WKY rats, but a significant incrase in pain sensitivity in SHR (table). 30 min after administration of 1 mg/kg propranolol, WKY and SHR did not differ significantly in their pain sensitivity (table). In contrast, injection of an α_2-adrenergic blocking drug, clonidine, 0.25 and 2.5 mg/kg, produced and analgesic effect (45–60% increase in latency time to the tail withdrawal reflex) which was not significantly different in SHR and WKY strains.

Our results demonstrate a low sensitivity to noxious stimuli in spontaneously hypertensive rats. The specific opiate antagonist naloxone eliminates the difference in pain sensitivity between hypertensive and normotensive rats, indicating that these changes could be related to differences in endogenous opiates or opiate receptors between the 2 strains.

A higher level of opioid activity has been reported in the spinal cord of experimentally hypertensive rats, which also present a decreased sensitivity to pain with respect to normotensive controls[8], indicating that hypertension might be generally associated with reduced sensitivity to pain.

The analgesia present in SHR can also be effectively blocked by l-propranolol, suggesting an involvement of endogenous catecholamines in this phenomenon. This mechanism might involve β-adrenergic, but not α_2-adrenergic receptors, since the analgesic effect of clonidine[14] was the same for both WKY and SHR.

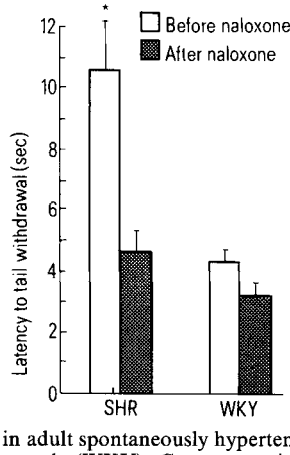
Our results could be related to central or peripheral mechanisms. In experimental hypertension, at least a central spinal opioid mechanism is involved[8]. Other possible central sites are some of the catecholamine-rich nuclei of the brain stem[5], such as the locus coeruleus. Activation of the locus coeruleus produces both analgesia and hypertension[15]. An interaction between morphine and endogenous catecholamines has long been demonstrated[16]. Drugs affecting catecholamine metabolism, such as monoamineoxidase inhibitors, potentiate the effects of morphine[17]. The β-adrenergic blocker propranolol is able to antagonize the analgesic effect of morphine[18]. An interaction between endogenous opiates and catecholamines could occur in SHR. The SHR present changes in noradrenergic and adrenergic neurons in several specific areas of the brain[4,19], and similar changes exist in experimentally hypertensive rats[20]. Changes in peripheral opiate metabolism could be associated with the alterations in peripheral catecholamine metabolism in hypertension[21]. Di Giulio et al.[22] reported decreased levels of enkephalins in peripheral organs of SHR, which may represent an increased turnover of endogenous opiates. Hypertensive animals can release higher amounts of catecholamines into the circulation when submitted to stress[23]. Peripheral administration of catecholamines enhances the analgesic effect of morphine, and this action is blocked by propranolol[18].

On the basis of the precedent information we can advance the hypothesis of an interaction between changes in catecholamine and opioid metabolism in the brain or peripheral tissues of hypertensive rats.

Effects of l-propranolol on the pain sensitivity of SHR and WKY rats

Treatment	Time of drug Administration before test	Latency to tail withdrawal (sec)	
		Wistar Kyoto	SHR
None		2.74 ± 0.51	12.84 ± 1.84*
Propranolol	15 min	2.11 ± 0.36	4.96 ± 0.43
Propranolol	30 min	2.68 ± 0.57	4.40 ± 0.98

Results represent jx ± SEM, for groups of 8 animals each, tested before and after administration of l-propranolol, 1 mg/kg, i.p. at 15-min intervals.
WKY + propranolol, 15 min = WKY + propranolol, 30 min = WKY, no drug = SHR + propranolol, 30 min = SHR + propranolol, 15 min < SHR, no drug, * $p < 0.01$ (Newmans-Keuls test)[13].



Pain sensitivity in adult spontaneously hypertensive rats (SHR) and normotensive controls (WKY). Groups consisted in 16 hypertensive and 16 normotensive rats. The animals were tested twice, 15 min apart, for their latency time to the tail withdrawal reflex (tail flick test)[12]. Hypertensive and normotensive animals were randomly distributed in 2 groups of 8 animals each, injected i.p. with saline (1 ml/kg b.wt) or naloxone (2 mg/kg) and tested again 30 min later. Results are expressed as $\bar{X} \pm$ SEM WKY + naloxone = SHR + naloxone = WKY control < SHR control. * $p < 0.01$ (Newmans-Keuls test)[13].

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