heart rate, blood pressure, and $\alpha$-adrenoceptor-mediated vasoconstriction when compared with normotensive subjects. The stress-induced increase in adrenaline was correlated with the attendant increase in blood pressure. The stress-induced reduction in forearm flow was reversed during infusion of the postjunctional $\alpha_1$-adrenoceptor blocker prazosin. Therefore, enhanced responses to sympathetic stress, as reflected and perhaps caused by an exaggerated rise in plasma adrenaline, may contribute to an increased $\alpha_1$-adrenoceptor-mediated vasoconstriction in essential hypertension.

Cardiovascular responses to stressful stimuli were found to be exaggerated and prolonged in patients with essential hypertension, particularly in those with borderline blood pressure values. In the established form of hypertension, we observed elevated plasma adrenaline concentrations which were directly related to the degree of $\alpha_1$-adrenoceptor-mediated vasoconstriction. We therefore investigated the effects of stressful sympathetic stimulation, as produced by the cold pressor test, on plasma adrenaline, heart rate, and blood pressure, as well as on forearm circulation, before and during postjunctional $\alpha_1$-adrenoceptor blockade with prazosin in patients with essential hypertension compared with normotensive subjects.

Material and Methods

Fifteen healthy volunteers, aged 31 to 62 years, with a casual diastolic blood pressure < 90 mm Hg (Korotkoff V) and 18 outpatients, aged 30 to 65 years, with established essential hypertension and diastolic pressures ≥ 100 mm Hg who were without treatment for at least six weeks, were selected. Informed consent was obtained from all individuals.

The studies started at 8 AM. After cannulation of the left brachial artery and of a right cubital vein, the patients were allowed to rest for 30 minutes. Thereafter, blood was drawn for the estimation of plasma adrenaline. Heart rate and intra-arterial pressure, as well as forearm blood flow measured by venous occlusion plethysmography, were recorded under basal conditions. These measurements were repeated immediately after cold pressor test, ie, immersion of the right hand in ice-water for one minute. The entire procedure was repeated 30 minutes later, after a ten-minute infusion of the selective postjunctional $\alpha_1$-blocker prazosin, 0.5 $\mu$g/min/100 ml of forearm tissue, a dose known to produce maximal regional vasodilation without causing systemic effects.

Results

As shown in Figure 1, plasma adrenaline, mean blood pressure, and heart rate were higher in the patients both before and during the cold pressor test; the percentage increase in plasma adrenaline correlated with the rise in mean blood pressure ($r = 0.514, p<0.05$). Before prazosin administration, forearm blood flow fell during the cold pressor test in both groups, starting from a higher basal level in the patients (Fig 2, upper panel). Infusion of prazosin increased forearm blood flow in both groups and to a greater extent in hypertensive patients (Fig 2, lower panel). When the cold pressor test was superimposed on postjunctional $\alpha_1$-blockade, there was a further increase in forearm blood flow, again this flow increase being more pronounced in hypertensive patients.
**DISCUSSION**

Patients with established essential hypertension not only exhibited higher plasma-adrenaline concentrations, heart rates, and α₁-adrenoceptor-mediated vasoconstriction under basal conditions, but also reacted with exaggerated sympathetic responses to the painful cold pressor stress. The stress-induced vasoconstriction was predominantly mediated via postjunctional α₁-adrenoceptors, since it could be blocked completely by prazosin. The reversal of the stress-induced reduction in forearm blood flow observed during prazosin infusion probably is due to an increase in flow secondary to the rise in blood pressure.

The elevated plasma adrenaline concentrations and their enhanced response to a stressful stimulus in hypertensive patients tally with earlier reports on resting levels and the demonstration of higher levels during each grade of sympathetic stimulation by physical exercise testing, thereby indicating elevated sympathoadrenal activity in these patients. Plasma adrenaline has been shown to correlate with the height of diastolic blood pressure, heart rate, and forearm vasoconstriction mediated by α₁-adrenoceptors or dependent on slow calcium channel influx. These relationships may be interpreted as adrenaline's being a marker of overall activity of the sympathetic nervous system or neurogenic vasoconstriction.

Prejunctional uptake of adrenaline and release together with noradrenaline may render the adrenaline a neurotransmitter in the strict sense of the word. Because of adrenaline's high affinity to prejunctional and postjunctional β-adrenoceptors and α₁-adrenoceptors, which also seem to be involved in postjunctional vasoconstriction, adrenaline may facilitate the predominantly β-adrenoceptor-mediated high cardiac output and high renal circulatory state in the early phase of hypertension, as well as being the trigger for the transition into a later β-hyporesponsive, predominantly α-adrenoceptor-mediated vasoconstrictor state of hypertension.

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Role of Opioid Peptides in Brain Mechanisms Regulating Blood Pressure

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Beta-endorphin and related opioid peptides are neuropeptides which appear to play a role in cardiovascular regulation which is supported by altered nociceptive responsiveness in hypertensive animals. In spontaneously hypertensive rats the pain threshold for electric stimulation is elevated; these rats show increased response latency time in a hot plate test. The opiate antagonist naloxone reverses these values to that of the normotensive controls. In other forms of experimental hypertension, eg, renal hypertension (one-clip, two-kidney model), no change in pain sensitivity is apparent. Sinoaortic baroreceptor denervation causes a labile hypertension without changes in hot plate response. Administration of beta-endorphin into the nucleus of the solitary tract (NTS) gradually decreases blood pressure and heart rate without affecting respiratory frequency. These cardiovascular effects are blocked by naloxone as well as by an antibody to beta-endorphin. In contrast to the effects of beta-endorphin, microinjection of enkephalins into the NTS increases blood pressure and heart rate. The data suggest the existence of two separate endorphin systems at the level of the NTS, one a depressor and another a pressor system. The depressor influence of beta-endorphin may play a role in the mechanism of action of antihypertensive agents such as methyldopa and clonidine. Our data support a role of endorphins as neuropeptides involved in cardiovascular regulation, exerting a dual influence at the level of the NTS.

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Opioid peptides such as beta-endorphin (LPH 61-91) and enkephalins belong to the already large number of brain-born peptides which are putative neurotransmitters or neuromodulators. A considerable number of peptidergic pathways, in particular in the brain stem, have already been described. The term neuropeptide was coined by De Wied. Neuropeptides affect a host of behavioral processes, such as learning and memory, and have been implicated in psychopathology. Evidence is now accumulating for a role of neuropeptides in central cardiovascular regulation, and angiotensin and substance P have been studied in this respect. The neurophysyseal peptides oxytocin and vasopressin inhibit brain pressor mechanisms, and since some of the fragments of vasopressin and oxytocin are as effective as the parent molecule, the inhibitory effect can be dissociated from the classic hormonal action of both peptides. Sites of action appear to be located in the limbic system and the more caudal brain stem structures.

Opioid peptides and opiate receptor sites are well represented in some brain stem and hypothalamic structures involved in cardiovascular regulation. The nucleus of the solitary tract (NTS), for example, contains opiate receptor sites, enkephalin perikarya, and terminals, and beta-endorphin-containing nerve fibers. Such brain structures may be sites where endorphins affect cardiovascular regulatory functions. An interesting observation by Zamir et al, showing a diminished response to noxious stimuli in genetically hypertensive SABRA strain rats, points to the possibility that increased activity is present in an opiate system in these hypertensive animals. In addition, in patients with essential hypertension a higher pain threshold in a toothpulp test was observed in comparison with normotensive control subjects.

Naloxone has been reported to reverse the hypotensive effect of clonidine and alpha-methyldopa in spontaneously hypertensive rats (SHR), and clonidine and alpha-methylnorpenephine have been shown to induce the release of a peptide with beta-endorphin-like immunoreactivity from brain stem slices of SHR. The antihypertensive action resulting from central alpha-adrenoceptor stimulation therefore may be due to the release of an endorphin-like peptide. The NTS appears to be a site of this hypotensive action of biogenic amines.

A central opiate pathway may exert a depressor influence in different shock states.

The responsiveness of hypertensive rats to noceptive stimulation and the effect of beta-endorphin and enkephalin on cardiovascular functions, when administered locally into the NTS, have been investigated.

NOCICEPTIVE RESPONSIVENESS OF HYPERTENSIVE RATS

To assess noceptive responsiveness a modified hot plate method was used. Rats were placed on a brass plate (54°C ± 0.1°C) within a perspex cylinder. The time elapsing before a first reaction was recorded as response latency time. Usually paw-licking was the first response, although in a few instances jerking with lifting of hind leg or jumping occurred as a first response. As shown in Figure 1 (left), spontaneously hypertensive rats (SHR) exhibited a longer latency time compared with age-matched normotensive Wistar Kyoto (WKY) controls. Systolic blood pressure of the SHR was in