47) Noradrenaline Release in the Brain of SHR Using Alpha-Receptor Agonists and Antagonists.

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The Spontaneously Hypertensive Rat (SHR) has proved to be an important animal model for essential hypertension in man. We have previously suggested that there are differences disagreement in the noradrenaline (NA) content of various brain regions between SHR and Wistar Kyoto rats (WKY). Abnormalities of the noradrenergic nervous system may underlie essential hypertension. It is well known that NA release is regulated by alpha-2 adrenergic receptor mediated autoregulation. The present study evaluates difference in endogenous NA release in the hypothalamus and pons + medulla oblongata of SHR and WKY using alpha-receptor agonists and antagonists.

METHODS: Four- and 12-week old rats (SHR, WKY) were killed by decapitation. The brains were rapidly removed, and pons + medulla oblongata and hypothalamus were dissected using the method of Glowinski and Iversen (1966), and cut sagittally into 0.4 mm thick slices, which were continuously superfused with Krebs medium containing pargyline 10uM for 60 min at 37°C. After 30 min of superfusion was added KCl(50mM). Endogenous NA content in the medium was measured at 10 min intervals using HPLC-ECD. DHBA (3,4-dihydroxybenzylamine) was added as an internal standard to the Krebs medium which contained (mM): NaCl,136; KCl,5.6; CaCl₂,2.2; NaH₂PO₄,1.2; NaHCO₃,16.2; glucose,5.5; ascorbic acid,0.29. Krebs medium was bubbled with 95 % O₂ and 5 % CO₂ in the present of tetrodotoxin-3uM and pargylin -10uM. The effects of yohimbine and prazosine as alpha- receptor antagonists and clonidine and fenilifline as alpha-receptor agonists were studied with Krebs medium for 60 min at 37°C. Each drug was added in three different doses (10⁻⁵,10⁻⁶,10⁻⁷M).

RESULTS: Amount of NA released from slices of both brain regions by addition of 50mM KCl did not significantly differ between SHR and WKY at 4 and 12 weeks. In the medium plus yohimbine (10⁻⁵,10⁻⁶M), endogenous NA release from the pons + medulla oblongata was decreased in SHR compared with WKY at 12-week. In the medium plus prazosine (10⁻⁵M), NA release from the hypothalamus was decreased in 4-week old SHR. The effects of other drugs in both brain regions of 4- and 12-week old SHR showed similar changes as in WKY.

DISCUSSION: In the present study, yohimbine as selective alpha-2 adrenoceptor antagonist potentiated NA release from both pons + medulla oblongata and hypothalamus of SHR and WKY. This suggests that the alpha-2 adrenoceptor mediates autoinhibition of the noradrenergic neurons in both brain regions. Noradrenergic neurons in the central nervous system, especially the pons + medulla oblongata and hypothalamus, are thought to play an important role in cardiovascular regulation. Our results indicate that the effect of yohimbine is smaller in the pons + medulla oblongata of SHR than in that of WKY, suggesting that alpha-2 adrenoceptor mediated autoinhibition of NA release is diminished in the pons + medulla oblongata of SHR, and thus that the alpha-2 adrenoceptor is altered in central noradrenergic neurons of SHR. Further, in both brain regions of SHR, the turnover of NA and dopamine- β -hydroxylase (DBH) activity decreased while binding of prazosine as alpha-2 receptor antagonist increased.

In summary, it seems from changes in endogenous NA release in both brain regions that abnormalities of central noradrenergic neurons may be possibly related to hypertension in SHR.