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Stimulation of the Aortic Baroreceptors, Enhance the Release of GABA to Locus Coeruleus (LC)

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LC is implicated in numerous CNS functions, including attention and arousal, cardiovascular regulation, antinociception, regulation of anxiety and stress response. The purpose of the present study was to define the role of the baroreceptor reflex to the LC function.

Male Sprague-Dawley rats (230-300 g) were used. A guide cannula was stereotaxically implanted under ketamine (50 mg/kg, i.p.) and sodium pentobarbital (40 mg/kg i.p.) anaesthesia. Target co-ordinates of the LC were (mm): AP 0.8 posterior to interaural line, 1.3 lateral from midline, DV 2.8 above the interaural zero plane. Chronic indwelling arterial and venous catheters were inserted. The aortic depressor nerve was bilaterally transected (AD). Sham-operated control rats received similar incisions leaving nerves intact. Five days after surgery, the stylet of the guide cannula was replaced by a push-pull cannula and the LC was superfused with artificial cerebrospinal fluid (CSF) at a rate of 28 µl/min. After an equilibration period of 80 min, superfusate was collected continuously in time periods of 3 min into tubes kept at -50^{0}C. At the end of the superfusion experiment, the brain was removed and the localization of the cannula was verified histologically. Pressor responses were elicited by noradrenaline (4 µg/kg/min i.v.). Depressor responses were elicited by nitroprusside (40-50 µg/kg/min, i.v.). The intervals between adjacent experiments were at least 60 min. Cardiovascular alterations were carried out at least 80 min after onset of superfusion. Amino acids released in the superfusate were determined by HPLC and fluorimetric detection after derivatization with o-phthaldialdehyde. Data were analysed statistically by Friedman's test followed by Wilcoxon's signed rank test for paired data. Lability is defined as the standard deviation of the blood pressure (BP). The standard deviation was calculated for each animal from sixty measurements carried out once per minute over a period of 1 h. Statistical analysis was carried out after logarithmic transformation. For comparison of labilities, basal BP, heart rates and release rates between sham-operated AD rats, Student's t-test for grouped data was used.

Superfusion of the LC with CSF started immediately after replacement of the stylet of the guide cannula by the push-pull micro-cannula. After reaching steady state, basal release rates of amino acids in the LC of sham-operated animals did not differ from this in AD rats. Mean arterial BP and heart rate in AD rats was significantly higher than in sham-operated animals. Similarly, the lability of arterial BP in AD animals was much more pronounced than in sham-operated rats. In sham-operated and AD rats, intravenous infusion of saline for 9 min did not influence either the release of amino acids in the LC or the BP. In sham-operated animals, intravenous infusion of noradrenaline for 9 min, led to a pronounced in-

crease in BP and bradycardia. The release rate of GABA was enhanced and the enhanced release lasted as long as the pressor response to noradrenaline. In AD rats, the pressor response to noradrenaline was less pronounced and lasted longer than in sham-operated rats. The rise in BP elicited by noradrenaline did not influence the release rate of GABA in the LC of AD rats. In both AD and sham-operated animals the release rate of glutamet (Glu) was unchanged. Intravenous infusion of nitroprusside for 9 min led to a pronounced fall of BP in sham-operated animals. In AD animals the effect of nitroprusside on the BP was more pronounced and lasted longer than in sham-operated animals. The fall of BP didn't influence the release rate of GABA in both sham and AD animals. On the other hand the fall of BP led to a slight increase of release rates of Glu in sham-operated animals and a more pronounced increase in AD rats.

It is well documented that baroreceptor activation diminishes LC activity. The responsible inhibitory neurotransmitter is GABA acting via GABA-A receptors. Our findings are in accordance with those of the others and that the GABA release is abolished in AD rats. On the other hand the paradox effect of higher release rate of Glu in AD rats can be excused by two different hypothesis. Glu is related more with emotional and less with baroreceptor stimuli. To the AD rats the organism is regulated to a higher level than in control animals and a drastic depressor response is a more potent stress stimulus thus elevating the release of Glu. Alternatively, the drastic fall in BP may decrease the blood flow in brain areas leading to ischemia and hypoxia and to the enhanced release of Glu in the LC. The other explanation is that the fall of BP due to NO donors is because the dilation of arteries as well as veins. Because of this there is a decrease of the total blood flow to the brain areas which can produce an acute ischemia and hypoxia and an increase to the release of glutamate.