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EFFECTS OF MELATONIN ON CARDIAC SYMPATHETIC FUNCTIONS AND B-ADRENERGIC PATHWAY IN THE SPONTANEOUSLY HYPERTENSIVE RATS
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Objectives: To determine whether reductions in mean arterial pressure (MAP) and heart rate (HR) induced by melatonin (MEL) in SHR are due to a modification of sympathetic functions and β-adrenergic receptor (ADR)-coupled adenylyl cyclase pathway in spontaneously hypertensive rats (SHR).

Methods: Eleven week old male SHR and WKY rats were treated or not with MEL (30 mg/kg/day) in drinking water during 4 weeks. Hemodynamic parameters were measured in conscious rats. The stimulation induced [3H]-norepinephrine release from isolated atria and cardiac β-ADR-coupled adenylyl cyclase pathway were assessed in SHR and WKY rats.

Results: The MAP and HR were decreased in MEL treated rats (p<0.05). The chronotropic response to isoproterenol was decreased in SHR compared to WKY rats but was increased in both groups of MEL treated rats (p<0.05) and thus normalizing the response of SHR. The plasma catecholamine levels were similar in SHR and WKY rats treated not with MEL. The stimulation induced [3H]-norepinephrine release from isolated atria was not altered by MEL. Total β-ADR density and affinity were similar in the heart of all 4 groups. However, when the relative density of the β1 and β2 subtypes was evaluated, the proportion of β2-ADRs was found to be increased in SHR before treatment (p<0.01) and the β1/β2 receptor proportions in SHR was restored to normal following a MEL treatment (p<0.01). The adenylyl cyclase reactivity to forskolin and to guanylylimidophosphate [Gpp(NH)p] did not differ in the four groups while the adenylate cyclase reactivity to isoproterenol was higher in SHR than in WKY before treatment (p<0.01). The Mel treatment increased the adenylyl cyclase reactivity in SHR and WKY rats (p<0.05).

Conclusion: This study suggests that the relative density of cardiac β-ADR is altered in SHR and that MEL treatment could restore to normal the β-adrenergic receptor proportion and potentiate the signaling pathway of these receptors. It is thus possible that MEL decreased the arterial pressure and increased the chronotropic response to isoproterenol through the potentiation of β-ADR-adenyl cyclase response.

Key Words: Sympathetic nervous system, Heart, Melatonin

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ENHANCED CONTRACTILITY OF RAT AORTA IN DOCA-SALT HYPERTENSION INVOLVES COX-2 ACTIVATION
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Responsiveness to many contractile agonists increase in deoxycorticosterone acetate (DOCA)-salt induced hypertension. We tested the hypothesis that enhanced contractility of rat aorta to norepinephrine (NE) in DOCA-salt hypertension is causally related to increased expression and activity of COX-2. Thoracic aortic rings were obtained from uninephrectomized rats fed for 3 weeks on either normal (control), or 8% sodium-potassium (experimental) diets. The control and experimental groups were implanted (s.c.) with placebo and DOCA (100 mg) 21-day release pellets, respectively. Tissue force of rings bathed with physiologic salt solution (PSS) (37°C; 5%CO2/95%O2) were measured with FT 03 force transducers coupled to a Grass polygraph. Tail cuff pressures (mmHg) were 180±5/166±5 (DOCA-salt) versus 128±3/116±6 (Control) rats. NE (0.001-1 μM) elicited contractions of endothelium-intact and denuded aortic rings; pD2 values for intact vessels were 7.04±0.05 (Control) and 8.14±0.05 (DOCA). NS-398 (3 μM), a COX-2-selective blocker, reduced NE contractions in Control (24±3%) and DOCA-salt (89±18%) aortic rings. Indomethacin (10 μM), a dual COX-1/COX-2 blocker, failed to alter NE contractions in the control, but reduced the contractions of DOCA hypertensive vessels by 46±5%. Piroxicam (10 μM), a COX-1-selective blocker did not alter NE contractions. Western blot analysis showed COX-2 immunoreactive bands (~70 kDa) and is significantly denser on densitometric units in DOCA-salt hypertensive versus control normotensive vessels. COX-1 protein expressions were not different in control normotensive and DOCA-salt hypertensive aortic vessels. We conclude: (1) that COX-2 expression increases significantly in DOCA-salt hypertension. (2) COX-2 mediates the production of a factor(s) that enhances rat aortic contractility.

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Key Words: DOCA-salt hypertension, COX-2 expression, Rat aorta

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INCREASED EXPRESSION OF GIA PROTEINS IN L-NAME-INDUCED HYPERTENSION IS REVERSIBLE BY LOSARTAN: IMPLICATION OF AT1 ANGIOTENSIN RECEPTOR
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We have previously reported that N-ω-nitro-L-arginine-methyl ester (L-NAME)-induced hypertensive rats exhibited an enhanced expression of Gia proteins. In addition, losartan, AT1 receptor antagonist, has been shown to decrease L-NAME-induced increase in the blood pressure. The present study was designed to evaluate the involvement of AT1 receptor in L-NAME-induced alterations in blood pressure and G-protein adenylyl cyclase signaling pathway. L-NAME (70 mg/kg body weight), Losartan (10 mg/kg b.wt) alone or in combination were given orally for 4 weeks. Control group received only plain tap water. The expression of Gia-2 and Gia-3 proteins and mRNA was enhanced in L-NAME-treated rats which was reversed by losartan treatment. However, losartan alone did not alter the levels of Gia α proteins or mRNA. On the other hand, the expression of Giaα was not altered by these treatments. Guanosine 5’-o-(3-thiophosphate) (GTPγS)– stimulated adenylyl cyclase activity in both control and L-NAME-treated groups, but the extent of stimulation was significantly attenuated in L-NAME-treated rats, which was reversed by losartan. Similarly, stimulation of adenylyl cyclase exerted by isoprotanol, 5'-N-ethylcarboxamidoadenosine (NECA) glucagon, forskolin and sodium fluoride were diminished in L-NAME-treated rats and were reversed by losartan treatment. On the other hand, inhibition of forskolin-stimulated enzyme activity by low concentrations of GTPγS that was significantly enhanced in L-NAME- treated rats, was attenuated by losartan. In addition, oxotremorine- and angiotensin II-mediated inhibition of adenylyl cyclase activity was completely attenuated in L-NAME-treated rats which was reversed by losartan. These results suggest the implication of AT1 receptor in L-NAME-induced enhanced expression of Gia proteins and hypertension.

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Key Words: Losartan, L-NAME-induced hypertension, G-protein-adenyl cyclase signaling