CORRELATIONS BETWEEN ARTERIAL HYPERTENSION INDUCED BY ANGIOTENSIN II AND SYSTEMIC INFLAMMATION IN RAT

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CORRELATIONS BETWEEN ARTERIAL HYPERTENSION INDUCED BY ANGIOTENSIN II AND SYSTEMIC INFLAMMATION IN RAT (Abstract): Angiotensin II has particularly shown to play a key role in the regulation of inflammatory processes in hypertension. Aim: The present study aims to correlate the angiotensin II – induced hypertension with systemic inflammation. Material and methods: We conducted an experimental study on Wistar male rats who received Ang II via subcutaneous miniosmotic pumps for 2 weeks. Rats were exposed to a 12h light /12h dark cycle. Sham rats were used as control. Systolic blood pressure measurements and a flow cytometric analysis of lymphocyte surface markers were performed. After 14 days, the animals were euthanized under anesthesia with xylazine/ketamine. Results: Systolic BP progressively and significantly increased in rats with Ang II chronic infusion. We observed a statistical significant difference (p = 0.00001), in terms of T lymphocytes percentage between control rats plasma and Ang II treated rats plasma, in 14 days. Conclusions: Angiotensin II is an important mediator of hypertension and directly promotes inflammation by noticeably increasing the quantity of T cells in kidney tissue. Keywords: ANGIOTENSIN II, HYPERTENSION, INFLAMMATION.

Hypertension is prevalent in 25% of the adult population and contributes to the development of coronary heart disease, stroke and chronic kidney disease (1). In 2003, the World Health Organization - International Society of Hypertension (WHO-ISH) provided a definition of hypertension as arterial pressure measurements of 140/90 mm Hg or greater (2). In only 5%-10% of patients, the causes of high blood pressure are identified. For the rest of cases the etiology remains unknown, and the hypertension is defined as “essential”. Numerous studies showed that renin angiotensin aldosteron system (RAAS) contributes to cardiovascular and renal homeostasis by generating angiotensin peptides, mainly angiotensin II (Ang II). It has been shown that increased levels of Ang II cause hypertension, cardiovascular hypertrophy (1), increased vascular reactivity to different vasoconstrictor agents (1,3), inflammation (4) and endothelial dysfunction (5). Ang II causes a mild increase in blood pressure having as results T cell activation and inflammation, these factors having as result a
sustained hypertension (6). The present study intends to highlight some correlations between arterial hypertension induced by angiotensin II and systemic inflammation.

**MATERIAL AND METHODS**

Male Wistar rats (250–260 g) (n=9) received Ang II (300ng/kg/min) in NaCl 0.9% via subcutaneous miniosmotic pumps, for 2 weeks as previously reported (7). Rats were exposed to a 12h light/12h dark cycle. Sham rats were used as controls (n=9). Care, use, and treatment of all animals in this study were in strict agreement with the guidelines of the animal care from the University of Medicine and Pharmacy "Grigore T. Popa" Iasi. Basal systolic blood pressure (SBP) measurements were performed for every rat by tail-cuff plethysmography, twice/week at a basal period. After 14 days the animals were euthanized under anesthesia with xylazine/ketamine and we collected blood samples. Flow cytometric analysis was used to study lymphocyte surface markers. Comparisons within groups were performed using paired Student’s t-test.

**RESULTS**

**Systolic blood pressure.** Before the treatments, systolic blood pressure was comparable in the two groups (~120 mmHg). Though, systolic BP gradually and significantly increased in animals with Ang II chronic infusion (208±2 mmHg for Ang II versus 120±5mmHg for control group, in the 14th day).

**Cellular viability in plasma.** In the Ang II treated rats plasma we observed a statistical significant increasing number of PI-positive cells (non-viable) compared to cells derived from control rat plasma (fig. 1).

The cellular viability in plasma from control rats, respectively Ang II treated rats, is shown in fig. 2 and 3.

**T and B lymphocytes into plasma.** In figures 4 and 5 we revealed the presence of T and B lymphocytes in rat plasma (control lot vs. Ang II lot). We observed a statistical significant difference (p = 0.00001), in terms of T lymphocytes percentage between control rats plasma and Ang II treated rats plasma, for 14 days (fig. 6). As shown in figure 7, the percentage of B lymphocytes plasma, was statistically significant higher on rats treated with Ang II for 14 days (p<<<0.05) compared to control lot.

![Cellular viability percentage in rats plasma (control; Ang II)](image)

**Fig. 1.** Cellular viability percentage in rats plasma (control; Ang II) (*p=0.002)
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**Fig. 2.** Cellular viability in plasma (control lot)

**Fig. 3.** Cellular viability in plasma (Ang II lot)

**T and B lymphocytes into plasma.** In figures 4 and 5 we revealed the presence of T and B lymphocytes in rat plasma (control lot vs. Ang II lot). We observed a statistical significant difference ($p = 0.00001$), in terms of T lymphocytes percentage between control rats plasma and Ang II treated rats plasma, for 14 days (fig. 6). As shown in figure 7, the percentage of B lymphocytes plasma, was statistically significant higher on rats treated with Ang II for 14 days ($p << 0.05$) compared to control lot.

**Fig. 4.** T and B lymphocytes in plasma (control lot)

**Fig. 5.** T and B lymphocytes in plasma (Ang II lot)
DISCUSSION

Hypertension should be considered as a potential multifactorial inflammatory disease. Morphological abnormalities in the renal parenchyma and arteries seem to determine hypertension. Inflammatory processes might induce renal vasoconstriction, ischemia and injury that could sustain systemic hypertension. Arterial and tubulointerstitial inflammatory cells infiltration in response to renal damage might further increase renal and vascular alterations through the production of oxidants and other soluble inflammatory mediators (7,8). Increased levels of blood pressure may induce proinflammatory and procoagulant responses.

Up-regulation of local and systemic inflammatory mediators, such as components of the renin-angiotensin system (RAS), endothelial adhesion molecules, chemokines, cytokines and tissue factor (TF), was demonstrated in essential hypertension (9,10,11). The renin angiotensin aldosteron system (RAAS) contributes to cardiovascular and renal homeostasis by generating angiotensin peptides, mainly angiotensin II (Ang II). The effector of the RAAS, angiotensin II, was known mainly as a humoral factor formed by the action of kidney-derived rate limiting enzyme renin (12).

Angiotensin II directly modulates cytokine release (13), endothelial adhesion molecule expression and the production of plasminogen activator inhibitor-1 (PAI-1) (14), thus favoring inflammatory vascular and renal damage (15, 16). These studies indicate that angiotensin II, in addition to its well-known cardiovascular effects, could also favor leukocyte recruitment within renal parenchyma in essential hypertension.

The flow cytometry results of the present study comparing control and Ang II treated animals noted that there is a statistically significant difference (*p = 0.00001) in the percentage of T lymphocytes in plasma derived from control group rats compared to the percentage of T lymphocytes derived from the plasma of Ang II treated group for 14 days. Also, the percentage of B cells was significantly higher in plasma of rats that were treated with Ang II for 14 days (*p <<< 0.05) compared to the percentage of B cells derived from the plasma of controls, confirming hypotheses from the literature regarding the involvement of angiotensin II in the development of inflammatory reactions.
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CONCLUSIONS

Our paper reports that T cells play an essential role in the genesis of hypertension and support the involvement of inflammation in the occurrence of this disease. In our study, angiotensin II increased T cell markers activation. Angiotensin II markedly increased the number of T cells in plasma. Thus T cells might represent a novel therapeutic target for the treatment of high blood pressure.

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REFERENCES


RELATIONSHIP OF CAFFEINE WITH ADIPONECTIN AND BLOOD SUGAR LEVELS IN SUBJECTS WITH AND WITHOUT DIABETES

Insulin resistance or abnormal insulin secretion, are the characteristics of type2 diabetes mellitus (DM2), resulting in a diminished body glucose disposal. Those with chronic hyperglycemia, insulin resistance, or DM2 are at greater threat for its associated risk factors like hypertension, dyslipidemia, and cardiovascular disease. Genetic background and diet are considered to be one of the risk factors for developing type2 diabetes. Interestingly, among the several factors present in diet, coffee is considered as a potent dietary-component associated with reduced risk of diabetes and its complications. Most generally consumed beverage is coffee in the world, and its beneficial effects on health have been attracting substantial consideration. The common protective effect of coffee against diseases like cancer, cardiovascular diseases and type 2 diabetes mellitus has been considered. Better glucose tolerance and a substantially lower risk of type 2 diabetes have been connected with high coffee consumption in diverse populations. The components responsible for the obvious beneficial effect of coffee on glucose metabolism remains blurred. Animal studies have shown that intake of the coffee components like chlorogenic acid, quinic acid and trigonelline, has enhanced glucose metabolism. Intervening metabolic studies on short term in humans have shown that caffeine can intensely lower insulin sensitivity. However, a regular high caffeine intake on long term has been linked with improved insulin sensitivity. An important secretory product of adipocytes is adiponectin, a marker and perhaps a mediator of metabolic and cardiovascular disease risk acts as a hormone with anti-inflammatory and insulin sensitizing properties. Further adiponectin levels are low in insulin-resistant subjects regardless of their obesity. A growing body of evidence has shown that high adiponectin levels confirm a protective effect against glucose intolerance budding in patients who are at high risk for diabetes. Further, it might be anticipated that the adiponectin level be affected with coffee consumption. In conclusion, the study shows the long term use of caffeine is more efficient on blood sugar and adiponectin levels, which needed in the prevention of complications in diabetic subjects (Bhaktha G, Nayak BS, Mayya S et al.Relationship of Caffeine with Adiponectin and Blood Sugar Levels in Subjects with and without Diabetes. Journal of Clinical and Diagnostic Research. 2015, Vol-9(1):1-3).

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