PERSPECTIVES IN HYPERTENSION

High-fat diet and hypertension: possible brain mechanisms involved

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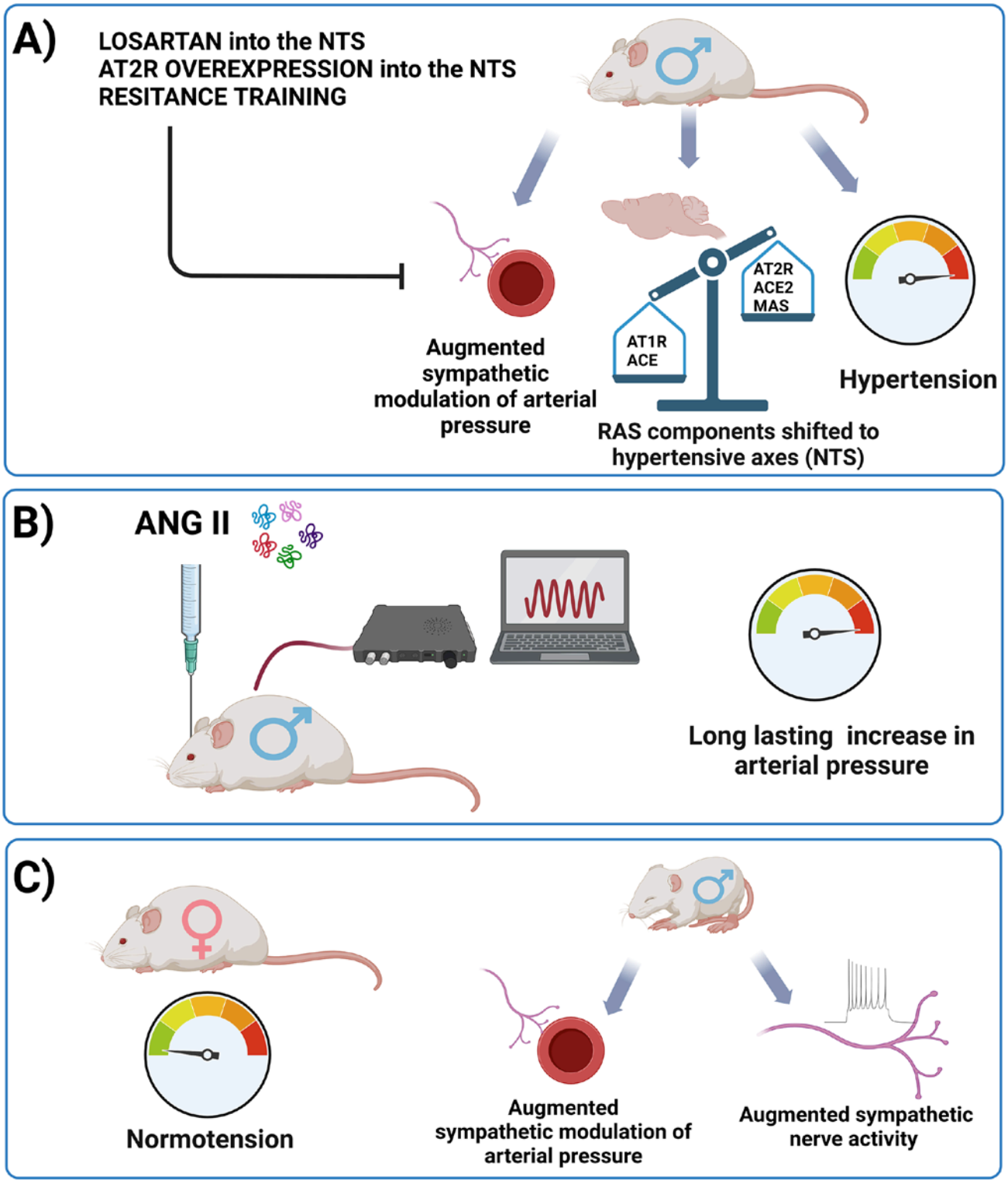
Obesity's burden has been seen around the globe.[1] The increase in the intake of highly caloric food and reduction in physical activity have been suggested to contribute to weight gain in the last decade.[2] One of the possible consequences of obesity is an increase in arterial pressure, and different mechanisms have been described as causing or facilitating hypertension, including increased activity in the renin-angiotensin-aldosterone system (RAS), sympathetic nerve activity, insulin and leptin, kidney dysfunction and baroreflex impairment.[3,4] If we consider the epigenetic effects, a considerable amount of research has demonstrated that children of obese mothers can develop obesity and hypertension, as shown in an excellent review from 2014.[5]

As a basic science and experimental scientist, I have been using animal models of disease, and became very interested in recent years to study the mechanisms underlying obesity-induced hypertension, particularly if the brain is involved. In addition, since peripheral renin-angiotensin-system (RAS) is involved with the increase in arterial pressure observed in obese subjects,[3] is there a role for the central RAS? Finally, is there any sexual dysmorphism and do the offspring of obese rat dams also have cardiovascular changes?

In a series of studies, my team and I observed that adult male and female rats fed for 6 weeks a high-fat diet (HFD; 45% calories from fat) had an increased body mass and adiposity, dyslipidemia, hyperinsulinemia and hyperleptinemia, similar to humans.[6-9] The juvenile male (around 35 days old – P35) offspring of HFD-fed dams also presented an increase in adiposity, despite no change in body weight at this age.[9] This age (P35) is equivalent to adolescence in humans. When we looked at the cardiovascular changes in adult male and female rats and juveniles we observed different responses. First, adult male rats had an increase in arterial pressure that started around 3 weeks after introducing the HFD and lasted for the whole experimental period, i.e., while being fed an HFD, male rats were hypertensive.[6] We also observed a higher modulation of sympathetic activity and a decrease in baroreflex sensitivity [6,7], which is also observed in obese humans.[3]

Since the increase in arterial pressure seems to have a neurogenic component, we targeted the nucleus of the solitary tract (NTS), located in the dorsal brainstem and very important to the control of cardiovascular regulation[10] to see if this was involved, particularly if the RAS in the NTS played a part. In the obese male rats, the gene expression of RAS components in the NTS was shifted to the hypertensive axis, i.e., angiotensin type 1 receptor (AT1R) and angiotensin-converting enzyme (ACE) were augmented. In contrast, angiotensin type 2 receptor (AT2R) and angiotensin-converting enzyme 2 (ACE2) were diminished.[7] Pharmacological blockade of AT1R in the NTS blocked the increase in arterial pressure and the modulation of sympathetic activity to the blood vessels and improved the baroreflex. In contrast, when we virally induced overexpression of AT2R in the NTS, the main effect observed was in the improvement of the baroreflex.[6] Since exercise has been proposed to be an effective approach to diminish the deleterious effect of high caloric/fat intake, resistance-trained HFD-fed rats had similar responses observed when AT1R was blocked and AT2R was overexpressed [7], suggesting a beneficial effect of resistance training in the deleterious changes in arterial pressure and brain RAS seen in HFD-fed rats.



However, not only the brainstem is involved in angiotension II (ANG II) responses. The injection of ANG II directly into the lateral ventricle in adult male rats induced a longer pressor response in HFD-fed rats when compared to standard diet (SD; 11% calories from fat) fed rats.[8] Therefore, the central RAS seems to be a pivotal mechanism involved in cardiovascular changes induced by a HFD in male rats **(Figure A and B panels)**. We then asked if the female rats had the same cardiovascular changes, and surprisingly, there was no change during the 6 weeks of the HFD

food regimen.[9] The absence of hypertension in female HFD-fed rats in our study may be related to the protective effect of estrogen. There was, however, an increase in heart rate, which is also similar to male rats.[9] Overall, it seems that there is a sexual dimorphism in the cardiovascular changes induced by HFD [9] **(Figure C left panel)**.

Finally, we focused on the offspring of obese dams, which were fed an HFD for 6 weeks before mating and during gestation and lactation (an additional 6 weeks). The male offspring were fed a SD after weaning (P21) to the day of the experiment (P35) and therefore, did not have access to HFD after birth. In spite of that, they presented a sympathoexcitation and a greater modulation of sympathetic activity to the blood vessels [9] **(Figure C right panel)**. The mechanism for these changes might be associated with blunted respiratory-related oscillations in sympathetic activity.[9] Taking together, brain mechanisms seem to be pivotal for the changes in arterial pressure/sympathetic activity in HFD-fed adult male rats and the juvenile offspring of HFD-fed dams.

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