



Review

Angiotensin II (de)sensitization: Fluid intake studies with implications for cardiovascular control



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HIGHLIGHTS

- Hypertension and cardiovascular disease are growing health concerns.
- Improper fluid balance is an underlying factor in hypertension.
- Drinking induced by angiotensin II (AngII) is an important model system.
- Repeated “pulsed” injections of AngII cause rapid desensitization.
- Pulsed injections appear to counteract the sensitizing effect of chronic AngII.

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ABSTRACT

Cardiovascular disease is the leading cause of death worldwide and hypertension is the most common risk factor for death. Although many anti-hypertensive pharmacotherapies are approved for use in the United States, rates of hypertension have increased over the past decade. This review article summarizes a presentation given at the 2015 meeting of the Society for the Study of Ingestive Behavior. The presentation described work performed in our laboratory that uses angiotensin II-induced drinking as a model system to study behavioral and cardiovascular effects of the renin-angiotensin system, a key component of blood pressure regulation, and a common target of anti-hypertensives. Angiotensin II (AngII) is a potent dipsogen, but the drinking response shows a rapid desensitization after repeated injections of AngII. This desensitization appears to be dependent upon the timing of the injections, requires activation of the AngII type 1 (AT_1) receptor, requires activation of mitogen-activated protein (MAP) kinase family members, and involves the anteroventral third ventricle (AV3V) region as a critical site of action. Moreover, the response does not appear to be the result of a more general suppression of behavior, a sensitized pressor response to AngII, or an aversive state generated by the treatment. More recent studies suggest that the treatment regimen used to produce desensitization in our laboratory also prevents the sensitization that occurs after daily bolus injections of AngII. Our hope is that these findings can be used to support future basic research on the topic that could lead to new developments in treatments for hypertension.

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1. Introduction

The annual meeting of the Society for the Study of Ingestive Behavior (SSIB) is heavily focused on feeding behavior. Although the name of the SSIB indicates that behavior is a primary focus, the inclusion of studies of metabolic disorders, including obesity, are welcomed at the meeting because of the general acceptance that these disorders are connected to feeding behavior, at least in some respects. Studies on fluid intake have become underrepresented at the annual meeting over the past several decades, not because these studies have been purposefully excluded from the scientific program, but because the number of scientists studying fluid intake seems to have decreased, whereas the number of scientists studying food intake seems to have increased. Nevertheless, each year, the annual SSIB meeting features some studies of fluid intake.

The relationship between obesity and food intake is analogous to the relationship between hypertension and fluid intake. Obesity results from a perturbation of energy homeostasis, whereas hypertension is a consequence of a perturbation of body fluid homeostasis. In this sense, studies on cardiovascular control and cardiovascular disease should be welcomed by the SSIB in the same way that studies of obesity and other metabolic disease states are featured at the meeting. From the SSIB's perspective, these topics are relevant because of their relationship

to ingestive behavior, but from a more general perspective, these topics are interesting because our research has the potential to improve health. This improvement matters to us, as human beings, because death is inevitable and it is natural to try to postpone that inevitability for as long as possible.

When we consider the causes of death, we can approach it from at least two perspectives: from a likely cause perspective (what is the most common cause of death) or from a risk factor perspective (what are the factors that best predict death). With respect to the former, cardiovascular disease is the leading cause of death in the United States [1] and worldwide [2]. An analysis of deaths in 187 countries in 2010, for instance, reports that of the 52.8 million deaths included in the analysis, 15.6 million of them (29.5%) were due to some form of cardiovascular disease [2]. From a risk factor perspective, hypertension is the single greatest risk factor for death [3,4]. In 2010, for example, 9.4 million deaths worldwide were attributable to high blood pressure [4] (Fig. 1, top).

Rates of hypertension among adults in the United States have risen significantly over the past decade (Fig. 1, bottom). This rise has occurred in spite of several FDA-approved treatments. These treatments are clearly imperfect, and do not work for every patient. Indeed, data from NHANES 2007–2010 indicate that a sizable proportion of the drug-

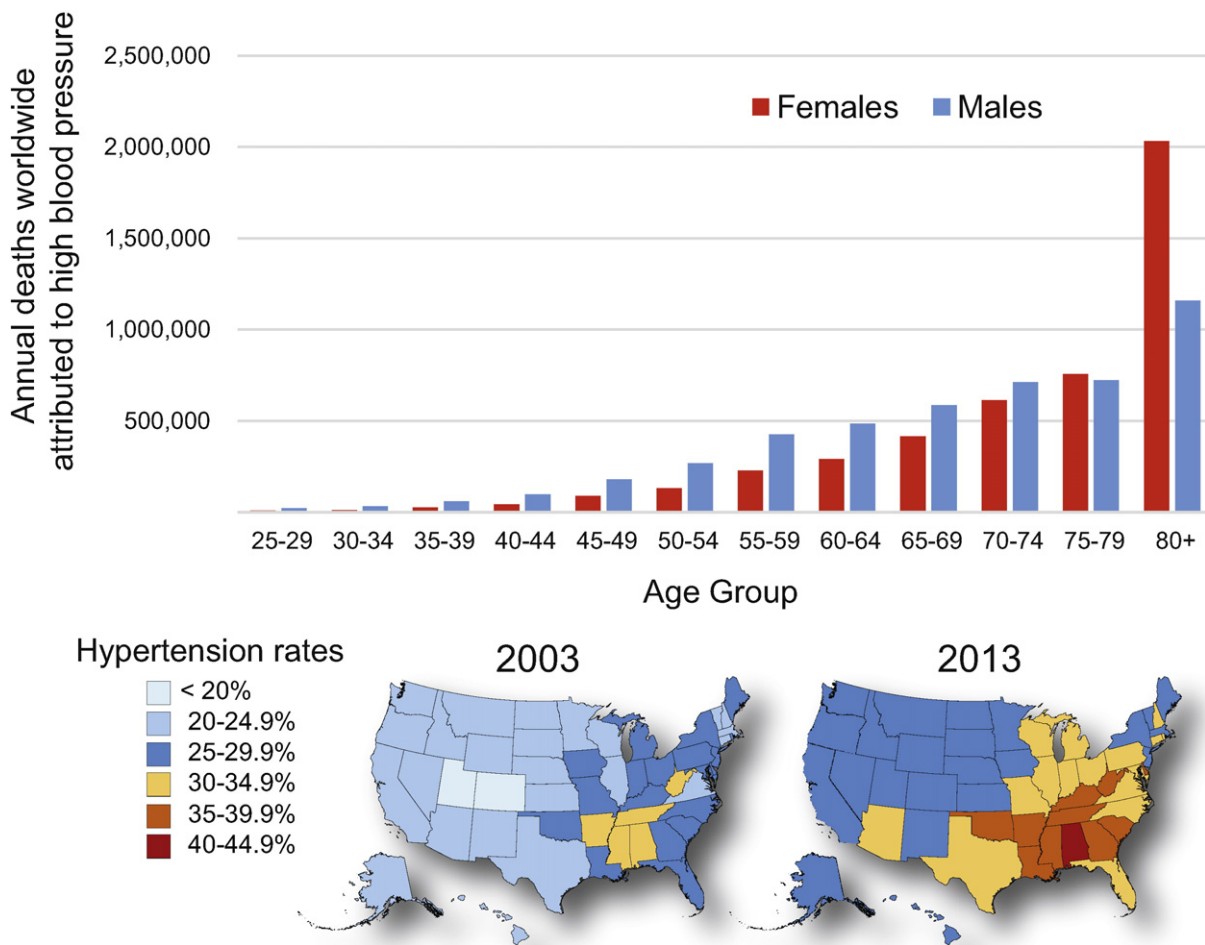


Fig. 1. Mortality and incidence rates of hypertension. Global deaths attributable to hypertension by age and sex in the year 2010 are shown in the top panel. The histogram was produced by data from [4]. Maps of the United States showing the change in the percent of the population with self-identified hypertension are shown in the bottom panel. Maps were generated using data from the Behavioral Risk Factor Surveillance System (BRFSS) conducted by the US Centers for Disease Control and Prevention (CDC). The map shows the percent of respondents over 18 years old who report ever having been told by a doctor, nurse, or other health professional that they have high blood pressure. Women who were told they had high blood pressure only during pregnancy, and respondents who were told they had borderline hypertension, were not included. Data were retrieved from <http://www.cdc.gov/cdi/>.

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