MEMORY MAY NOT BE THE FIRST THING TO GO: FOCUS ON “DRINKING AND ARTERIAL BLOOD PRESSURE RESPONSES TO ANGIOTENSIN II IN YOUNG AND OLD RATS” BY THUNHORST ET AL.

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The aging of the world’s population brings health problems that have the potential of exhausting health care resources, both financial and human. Many of these problems involve the debilitating results of age-related failure of organ systems and/or neurological function. In contrast, one of the most common health concerns in the elderly is a deceptively benign condition with potentially disastrous sequelae: dehydration. In the extreme, confusion, seizures, and death can result from uncorrected dehydration\(^2\). Even milder dehydration can impair resistance to and recovery from common ailments such as colds and flu, and promote or exacerbate respiratory and urinary tract infections that frequently occur in the elderly\(^2, 12\). Interestingly, the development of dehydration in the elderly is attributable not only to renal and/or endocrine dysfunction, but also to decreased fluid intake. More specifically, it appears that responsiveness to signals for thirst that are critical in stimulating fluid ingestion necessary for adequate hydration is diminished in the elderly. Thus, simple behavioral modifications can largely correct and, indeed, prevent, the adverse physiological and cognitive consequences related to severe dehydration. This strategy has been the underpinning of numerous interventional programs, particularly those targeted toward elderly populations residing in nursing homes. However, better understanding and treatment of this condition ultimately will derive from animal studies, in which experimental manipulations and testing strategies that are not feasible in humans may be employed.

In a paper entitled “Drinking and arterial pressure responses to angiotensin II in young and old rats” published in the current issue of American Journal of Physiology, Thunhorst and colleagues\(^{10}\) advance our understanding of the phenomenon of attenuated thirst in dehydrated elderly in two important ways. First, the authors focus on hypotension, such as may ensue after hypovolemic dehydration, rather than on osmotic dehydration. Clearly, both decreased volume and increased osmolality contribute to dehydration and, in fact, a wealth of information is available about the hormonal and physiological signals specific to each that trigger thirst in younger subjects, as well as about the receptor mechanisms by which the behavioral responses are initiated\(^{6-7}\). However, the majority of previous studies of
dehydration in elderly humans have concentrated on the osmotic aspects of dehydration\textsuperscript{e.g.,(4)}, as have many in elderly animals\textsuperscript{e.g.,(13)}. Thus, these studies by Thunhorst and colleagues focusing on hypovolemia and hypotension allow better understanding of age-related deficits in compensatory behavioral responses to the complex challenge(s) to body fluid balance inherent in dehydration. Secondly, the authors integrate findings from related disciplines to build upon their own previous work showing blunted drinking by aged rats in response to hypotension\textsuperscript{(11)} and investigate the mechanism that underlies reduced responsiveness to signals related to hypovolemia-hypotension thirst, such as angiotensin II. Previous studies report a reduction in stimulated renin release in aged rats\textsuperscript{(1)}. Thus, the authors sought to determine whether the age-related attenuation of water intake stimulated by hypotension in aged rats is attributable solely to deficiencies in the biosynthesis of angiotensin II, or whether decreased responsiveness to elevated circulating levels of angiotensin II also plays a role. An important aspect of this determination was to control for other factors that could influence behavioral responses to hypotension and/or hypovolemia. It has been reported that blood pressure influences drinking responses\textsuperscript{(9)}, and that aging alters cardiovascular responses to angiotensin II\textsuperscript{(3)} due to impairments in baroreflex-mediated buffering of heart rate and sympathetic nerve responses to changes in blood pressure\textsuperscript{(5)}. Accordingly, the authors pharmacologically ‘clamped’ blood pressure to minimize effects on water intake secondary to age-related differences in blood pressure and baroreflex input to central areas important in drinking responses.

The results of these thoughtful and carefully controlled studies are clear: when rats were infused intravenously with angiotensin II at physiological doses and rates that produce a slow, sustained hypertension of comparable magnitude among the three age groups (young – 4 months; middle-aged – 12 months; old – 29 months), there was no effect of age on the stimulated water intake. In contrast, when the angiotensin II-induced increase in blood pressure was prevented by co-infusion with the vasodilator, minoxidil, water intake by young rats increased, whereas that by both middle-aged and old
rats was unaffected. In short, when age-related differences in renin release stimulated by hypotension were eliminated by infusion of exogenous angiotensin II, deficits in drinking by aged rats were eliminated. Nonetheless, baroreflex activation did not appear to restrain water intake in aged or middle-aged rats, as it did in young rats. Thus, the results of these studies complement reports of blunted drinking by aged rats in response to osmotic dehydration\(^{(13)}\) and reinforce earlier findings that water intake stimulated by hypovolemic dehydration is impaired in aged rats. Moreover, in conjunction with previous studies, these results suggest that aging influences two opposing factors that determine water intake in response to hypotension. Release of angiotensin II, the excitatory factor, is impaired in aged rats\(^{(1)}\), and the inhibition provided by baroreflex input, which limits angiotensin II-induced water intake, appears to be impaired in both aged and middle-aged rats. More importantly, however, despite the apparent reduction in sensitivity to inhibitory baroreflex input, neither middle-aged nor aged rats drank more in response to angiotensin II infusion than did young rats. This observation suggests that responsiveness to an excitatory signal for ‘hypovolemic-hypotensive thirst’ also is impaired by aging. Thus, the significance of these studies is more than the confirmation of an observation of another deficit in the behavioral response to a specific aspect of dehydration. Rather, these studies have revealed a potential mechanism that underlies a common health concern in the elderly: decreased responsiveness to angiotensin II that may contribute to dehydration via a diminished excitatory signal for thirst.

One of the hallmarks of a good study is that the questions which inevitably remain are clear. So it is with this study. One obvious question is whether age-related impairments in angiotensin II release, in responsiveness to the excitatory effects of elevated angiotensin II, and in responsiveness to the inhibitory influence of baroreceptor activation occur simultaneously or develop at different ages. And if the latter, at what ages and by what mechanism(s)? Other avenues for future investigation include the possibility that the attenuated drinking by aged rats during hypotension and/or hypovolemia also may involve decrements in the sensitivity to excitatory effects of decreased blood pressure independent of
angiotensin II and, more specifically, age-related decrements in the excitatory effect of baroreceptor unloading, such as occurs during hypotension or hypovolemia. In addition, given that dehydration typically involves both a volume and an osmotic component, it would be of great interest to evaluate the effect of aging on behavioral responses to combined osmotic and hypovolemic dehydration. Finally, in addressing the specifics of how the decreased responsiveness to angiotensin II may occur, the subfornical organ emerges as a likely area within the central nervous system upon which to focus see, e.g., (8). The possibility of changes in angiotensin II receptor number or sensitivity within the subfornical organ not only may lead to further understanding of the mechanisms underlying age-related deficits in drinking stimulated by hypotension or hypovolemia, but also may allow the eventuality of targeted clinical interventions.
REFERENCES


