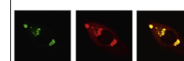


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## Research Report

# Acute repeated intracerebroventricular injections of angiotensin II reduce agonist and antagonist radioligand binding in the paraventricular nucleus of the hypothalamus and median preoptic nucleus in the rat brain



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## ABSTRACT

Angiotensin II (Ang II) stimulates water and saline intakes when injected into the brain of rats. This arises from activation of the AT<sub>1</sub> Ang II receptor subtype. Acute repeated injections, however, decrease the water intake response to Ang II without affecting saline intake. Previous studies provide evidence that Ang II-induced water intake is mediated via the classical G protein coupling pathway, whereas the saline intake caused by Ang II is mediated by an ERK 1/2 MAP kinase signaling pathway. Accordingly, the different behavioral response to repeated injections of Ang II may reflect a selective effect on G protein coupling. To test this hypothesis, we examined the binding of a radiolabeled agonist (<sup>125</sup>I-sarcosine<sup>1</sup> Ang II) and a radiolabeled antagonist (<sup>125</sup>I-sarcosine<sup>1</sup>, isoleucine<sup>8</sup> Ang II) in brain homogenates and tissue sections prepared from rats given repeated injections of Ang II or vehicle. Although no treatment-related differences were found in hypothalamic homogenates, a focus on specific brain structures using receptor autoradiography, found that the desensitization treatment reduced binding of both radioligands in the paraventricular nucleus of the hypothalamus (PVN) and median preoptic nucleus (MnPO), but not in the subfornical organ (SFO). Because G protein coupling is reported to

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have a selective effect on agonist binding without affecting antagonist binding, these findings do not support a G protein uncoupling treatment effect. This suggests that receptor number is more critical to the water intake response than the saline intake response, or that pathways downstream from the G protein mediate desensitization of the water intake response.

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## 1. Introduction

Angiotensin II (Ang II) potently stimulates drinking behavior. Repeated injections of Ang II have different effects, dependent upon the timing of the injections. Specifically, daily injections of Ang II or continuous infusion over days sensitizes its dipsogenic and natriorexigenic potencies (Bryant et al., 1980; Moellenhoff et al., 2001; Pereira et al., 2010), but acute repeated injections within a shorter timeframe desensitize the water intake response normally observed after Ang II injection (Quirk et al., 1988; Torsoni et al., 2004; Vento et al., 2012). Interestingly, the behavioral desensitization caused by acute repeated injections of Ang II is selective to the water intake effects of the peptide, with no observed desensitization of saline intake (Vento and Daniels, 2010a). This is potentially informative because previous studies using cell culture models suggested that the mechanism of desensitization relied heavily on receptor internalization (Hein et al., 1997; Mehta and Griendling, 2007; Thomas et al., 1998); however, this internalization would likely affect intake of both saline and water, since the receptors would no longer be able to bind extracellular Ang II.

Another mechanism of desensitization involves the dissociation of G proteins from G protein-coupled receptors in response to agonist binding (Bonde et al., 2010; Crane et al., 1982; Poitras et al., 1998; Speth and Kim, 1990). In such cases not only is there a loss of connectivity with the G protein transducer, there is also a reduction in agonist binding

affinity (Crane et al., 1982; Glossmann et al., 1974; Rodbell et al., 1971; Speth and Kim, 1990).

By examining the binding of an agonist angiotensin analog  $^{125}\text{I}$ -Sar<sup>1</sup> Ang II, versus a classical antagonist angiotensin analog,  $^{125}\text{I}$ -Sar<sup>1</sup>,Ile<sup>8</sup> Ang II, it should be possible to determine whether the desensitization of the dipsogenic response to intracerebroventricular (ICV) Ang II (Vento and Daniels, 2010a) occurs via uncoupling of the G protein (decreased  $^{125}\text{I}$ -Sar<sup>1</sup> Ang II binding with no change in  $^{125}\text{I}$ -Sar<sup>1</sup>,Ile<sup>8</sup> Ang II binding) or a G protein-independent mechanism. Possibilities for G protein-independent mechanisms include receptor internalization, in which case both the agonist and antagonist radioligand binding should decrease, or a decrease in signaling pathways downstream from the G protein, in which case radioligand binding may not change. The present studies used this strategy to test the hypothesis that changes in G protein coupling are responsible for the behavioral effects of repeated injections of Ang II.

## 2. Results

A two-way repeated measures ANOVA was run to determine if the repeated exposures to Ang II selectively reduced the binding affinity of the agonist radioligand in hypothalamic tissue membranes (Table 1). As shown in Fig. 1A, there was no reduction in radioligand binding affinity for either the agonist

**Table 1 – Statistical Analysis of radioligand binding assays of hypothalami from angiotensin II desensitized and control brains.**

Condition	$K_d$	$B_{max}$	Bound
SAR control	$3.94 \pm 1.2$	$823 \pm 220$	$100 \pm 8.3$
SAR desensitized	$1.93 \pm 0.55$	$476 \pm 120$	$96 \pm 5.6$
SI control	$1.21 \pm 0.23$	$425 \pm 75$	$121 \pm 10$
SI desensitized	$0.96 \pm 0.16$	$360 \pm 60$	$119 \pm 8.1$
<b>F values</b>			
Treatment	$F_{1,10} = 3.35$	$F_{1,10} = 5.55$	$F_{1,10} = 0.20$
Radioligand	<b><math>F_{1,10} = 8.62</math></b>	<b><math>F_{1,10} = 3.39</math></b>	<b><math>F_{1,10} = 16.6</math></b>
Interaction	$F_{1,10} = 2.10$	$F_{1,10} = 1.52$	$F_{1,10} = 0.09$
<b>P values</b>			
Treatment	0.0973	0.0955	0.6668
Radioligand	<b>0.0149</b>	<b>0.0403</b>	<b>0.0022</b>
Interaction	0.1784	0.2461	0.769

Bolded values are statistically significant ( $p < 0.05$ ). SAR,  $^{125}\text{I}$ -Sar<sup>1</sup> Ang II; SI,  $^{125}\text{I}$ -Sar<sup>1</sup>,Ile<sup>8</sup> Ang II.

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