7-19-2008

Transcriptional regulation network analysis of the hypertension-perturbed nucleus tractus solitarius

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BMC Neuroscience

Poster presentation

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from Seventeenth Annual Computational Neuroscience Meeting: CNS*2008
Portland, OR, USA. 19–24 July 2008

Published: 11 July 2008

BMC Neuroscience 2008, **9**(Suppl 1):P31 doi:10.1186/1471-2202-9-S1-P31

This abstract is available from: http://www.biomedcentral.com/1471-2202/9/S1/P31

Introduction

Neurons expressing the angiotensin II (angII) AT1 receptor (AT1R) in the nucleus tractus solitarius (NTS) have been implicated in many of the functions assigned to angII in the CNS including roles in neural control of cardiovascular function, in particular blood pressure regulation, the baroreflex, stress responses and maintenance of homeostasis (thirst and salt appetite). AngII, acting through the AT1 receptor has two main effects on neurons: a rapid and transient modulation of K+ and Ca2+ currents and longer lasting changes in gene expression, ultimately leading to modulation of noradrenergic neuronal networks regulating cardiovascular function [1]. Using a combined experimental and computational systems level analysis, we have investigated the transcriptional regulatory network downstream of AT1R activation by using N1E-115 neuroblastoma cells engineered to express AT1Rs as a model system and have recently extended this to the NTS.

Methods

We have applied transcriptional regulatory network analysis (TRNA), using our bioinformatics framework, Promoter Analysis and Interaction Network Toolset (PAINT) [2] to the response of the NTS both directly to angII and to phenylephrine-induced acute hypertension. TRNA makes the fundamental assumption that many co-expressed genes share transcription regulatory elements (TRE's), typically transcription factor binding sites, in their promoters, leading to co-regulation. This results in a higher frequency of the suspect binding sites in the promoters of sets of co-regulated genes relative to randomly associated sets of genes. PAINT uses bioinformatics in combination with robust statistical approaches to identify those regulatory elements significantly enriched in the promoters of the genes of interest relative to random gene sets. Predicted TF:promoter interactions are tested using chromatin immunoprecipitation PCR (ChIP-PCR) with chromatin from untreated and perturbed (angII or hypertension) NTS or cell lines.

Results and conclusions

TRNA predictions generated from microarray-based gene expression analysis of stimulated NTS *ex vivo* by 100 nM angII for 4 hours (n = 4) are shown in Table 1. Predicted TF's include those previously described as angII-responsive in neurons (CREB, KROX), angII-responsive in non-neuronal cells (E2F, ATF and MEF2), and novel associations (Pax, cRel). Validation studies using chromatin immunoprecipitation (ChIP) to test specific TF::promoter interactions in the *in vivo* NTS and in an engineered AT1R-expressing neuronal cell line (N1E-AT1). Several predicted interactions have been confirmed, demonstrating both angII and hypertension-dependent binding dynamics. TRNA has successfully predicted TF activity dynamics at specific promoters relevant to neuronal function in hypertension and angII perturbed NTS. Going forward, these validated interactions will be manipulated *in vivo* to directly demonstrate a role in CNS cardiovascular regulation.

Table 1: TRNA of AT1R-dependent NTS Expression

TF Family	Enriched TRE	Fisher's p-value
CREB	V$CREB_Q2_01	0.045
ATF	V$ATF1_Q6	0.016
ATF	V$ATF3_Q6	0.035
ATF	V$ATF6_01	0.027
E2F	V$E2F1_Q3_01	0.016
MEF2	V$ZID_01	0.0065
Pax	V$PAX3_B	0.0012
cRel	V$CREL_01	0.0023
KROX/egr1	V$KROX_Q6	0.036

Acknowledgements

The authors wish to acknowledge the expert technical assistance of H. Liu, Y. Liu and M. Payne in support of these studies and the intellectual input of the other members of the Daniel Baugh Institute for Functional Genomics and Computational Biology. This work was supported by grants from the NIGMS and NHLBI (J. Schwaber, PI).

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