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Biomedical Sciences, Department of

2015

PACAP and Cocaine Reinstatement: A Neuropeptide Expressed by Corticostriatal Neurons that Regulates Nucleus Accumbens Astrocytes

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Recommended Citation

Kong, Linghai; Hess, E.; Maunze, Brian; Hurley, Matthew M.; Makky, Khadijah; Choi, Sujean; Mantsch, John R.; and Baker, David A., "PACAP and Cocaine Reinstatement: A Neuropeptide Expressed by Corticostriatal Neurons that Regulates Nucleus Accumbens Astrocytes" (2015). *Biomedical Sciences Faculty Research and Publications*. 159.

https://epublications.marquette.edu/biomedsci_fac/159

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Presentation Abstract

Program#/Poster#: 411.21/L21

Presentation Title: PACAP and cocaine reinstatement: A neuropeptide expressed by corticostriatal neurons that regulates nucleus accumbens astrocytes

Location: Hall A

Presentation time: Monday, Oct 19, 2015, 1:00 PM - 5:00 PM

Presenter at Poster: Mon, Oct. 19, 2015, 1:00 PM - 2:00 PM

Topic: ++C.17.h. Cocaine: Behavioral studies

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Abstract: Drug addiction involves heightened relapse vulnerability arising from persistent drug-induced neuro-adaptations, including a) hypofrontality which is thought to reflect reduced firing of cortical afferents to the nucleus accumbens (NAcc) and b) altered glutamate homeostasis in NAcc that likely involves reduced glutamate release and uptake by astrocytes. An important question is whether these forms of pathological plasticity are functionally linked such that reduced corticostriatal firing may result in aberrant regulation of astrocytes in the NAcc. To begin to evaluate this possibility, we first determined whether neurons regulate system xc⁻ (Sxc) activity, a mechanism of non-vesicular glutamate release by astrocytes. We found that the rate of Sxc activity in astrocyte cultures was significantly increased in cells exposed to neuronal conditioned media achieved using neuronal inserts. These experiments demonstrate that releasable neuronal factors significantly upregulate Sxc activity. We hypothesize that the pituitary adenylyl cyclase activating peptide (PACAP) may be the neuronal factor regulating glutamate release by astrocytes involving Sxc. First we determined that PACAP mimics a neuronal insert in that it significantly

upregulates Sxc activity in astrocytes. Next, we verified the expression of PACAP in neurons from the prefrontal cortex (PFC) projecting to NAcc. Together, these data support the hypothesis that reduced corticostriatal firing may result in decreased PACAP release in NAcc which could potentially blunt Sxc activity in NAcc astrocytes. To determine whether this would impact relapse vulnerability, we microinjected PACAP into the NAcc and found that this significantly reduced cocaine-primed reinstatement, suggesting that increased PACAP signaling, consistent with other approaches capable of increasing Sxc activity, may blunt relapse vulnerability. In order to determine whether reduced PACAP signaling is sufficient to increase relapse vulnerability, we microinjected the PAC1R inhibitor PACAP6-38 into the NAcc. Preliminary data indicate that this is sufficient to produce an increase in cocaine reinstatement. Collectively, these studies demonstrate that neuropeptide PACAP is a powerful regulator of cocaine-related behaviors, likely through the modulation of glutamate homeostasis as maintained by astrocytes. As a result, an unrecognized consequence of hypofrontality may be impairing neuron-astrocyte interactions in a manner that determines the magnitude of relapse vulnerability.

Disclosures: **L. Kong:** None. **E. Hess:** None. **B. Maunze:** None. **M. Hurley:** None. **M. Khadijah:** None. **S. Choi:** None. **J. Mantsch:** None. **D. Baker:** None.

Keyword (s): ASTROCYTE

system xc-

PACAP

Support: DA025617 (DB)

DA035088 (DB and SC)

DK074734 (SC)

DA15758 (JM)