IN BRIEF…

Manganese, a friend or foe to dopaminergic neurons?

GD Stanwood, **DB Leitch**, V Savchenko, J Wu, VA Fitsanakis, DJ Anderson, **JN Stankowski**, M Aschner, B McLaughlin (2009). Manganese exposure is cytotoxic and alters dopaminergic and GABAergic neurons within the basal ganglia. *J Neurochem*. **110** (1): 378-89.

Manganese is a naturally occurring element essential for the proper metabolism of amino acids, protein and lipids. It is crucial for maintaining proper cellular functioning including maintenance of redox states, facilitating protein conformation, modulating ion and energy homeostasis and overall signal transduction in neurons. Over exposure to manganese can result in various irreversible neurological phenomenon such as motor symptoms similar to that of Parkinsons, dystonia and gastrointestinal tract dysfunction. In this study, the authors explored the neurotxic potential of manganese in dopaminergic neurons *in vivo* in mice, looking especially at the vulnerability of nigrostrial pathways. They found that manganese chloride exposure, even at subtoxic doses changed the neuronal cytoskeleton of dopaminergic neurons. When the manganese treatment was extended to a period of 30days, a 20% reduction in TH-posiive neurons was observed in the substantia nigra pars compacta (SNpc), quantified by a widespread reduction in SNpc cell numbers through Nissil body staining. Parts of the basal ganglia including the striatum were also affected during treatment, showing sensitivity to nigrostriatal pathways. This study provides chronicles the timely repercussions of acute and chronic manganese exposure and provides an explanation for the motor manifestations observed from manganese intoxification.

How quickly can you detect a face? Temporal dynamics within neural constructs involved in the detection of familiar and novel faces

Blackford JU, **Avery SN**, Shelton RC, Zald DH. (2009). Amygdala temporal dynamics: temperamental differences in the timing of amygdala response to familiar and novel faces. *BMC Neurosci*. 10:145.

Inhibited temperament involves a predisposition of individuals to respond to new people, places or things with wariness or avoidance behavior, a characteristic trait known to be associated with increased risk for social anxiety disorder and major depression. Within the human brain, functional magnetic resonance imaging (fMRI) has shown the magnitude of blood oxygen level dependent (BOLD) responses in the amygdala for novel stimuli to be associated with inhibited temperament. The authors in this study used an event related fMRI paradigm to investigate the temporal dynamics (latency, duration and peak) of the BOLD response to novel stimuli within the amygdala. They presented both novel and familiar faces to both inhibited and uninhibited temperament populations. Results indicated that the amygdala in inhibited participants responded faster to novel faces than familiar faces. In addition, they found that the inhibited participants showed both a longer and greater amygdala response to all faces in comparison to the uninhibited population, even though there were no differences in the peak BOLD response. Blackford and colleagues speculate that this temporal computational bias for novel stimuli within the amygdala may lead to greater neophobic responses and could allude to a plausible mechanism for the development of social anxiety.

apoptosis during embryogenesis. The rapid and controlled clearance of these dead cells is vital, as non-ingested cells can generate inflammation and detrimental immune responses.

In a recent *Nature Neuroscience* article, a team led by Bruce Carter recognizes a specialized glial cell, satellite glial cell precursors (SGC), in the clearance of dead neurons in the dorsal root ganglia of embryonic mice. Previously, it was unclear which cells were responsible for apoptotic clearance, with default responsibility handed to macrophages. However, through confocal and electron microscopy and *in vitro* assays, the group demonstrates that the vast majority of apoptotic neurons are associated or engulfed within SGC's, highlighting an unrecognized role for glial cells in phagocytosis.

In addition, the group provided a potential molecular mechanism for engulfment of dead cells. Jedi-1 and MEGF10, homologues of known *c. elegans* and *Drosophila* proteins, are expressed in the brain and specifically within SGCs in the DRG. Transient expression of the either protein in cultured HEK cells led to binding of neuronal corpses, and overexpression of the proteins in glial cells leads to increased engulfment of dead cells, suggesting a clear role for Jedi-1 and MEGF10 as engulfment receptors. Through their research, Wu et al establish satellite glial cell precursors as members of the 'clean-up' crew in the peripheral nervous system, performing a similar role as microglia in the brain, and importantly implicate two receptors as crucial sensors in the proper clearance of apoptotic cells.

Original Research Article:
HH Wu, E Bellmunt, **JL Scheib**, V Venegas, C Burkert, LF Reichardt, Z Zhou, I Fariñas, BD Carter (2009). Glial precursors clear sensory neuron corpses during development via Jedi-1, an engulfment receptor. *Nat Neurosci.* **12** (12): 1534-1541.

Bad huntingtin, protective effect

Huntington's disease (HD) is a unique neurodegenerative disorder in that it has been mapped to a single locus, the *huntingtin* gene. In the disease, huntingtin protein progressively undergoes an expansion of a polyglutamate region. Onset of symptoms correlates with a specific number of polyglutamate repeats, such that the disease progressively worsens with age. Thus far, research has been unable to explain how mutant huntingtin leads to a remarkably specific loss of medium spiny neurons in the striatum, a primary cause of the motor deficits seen in patients. One hypothesis is that striatal neurons are situated in an environment that may uniquely impact their vulnerability to mutant HTT; a

recent paper from the Bowman lab investigates this gene-environment hypothesis in the context of HD, with specific focus on the impact of metal neurotoxicology.

Williams *et al*. performed a disease-toxicant interaction screen in order to test a correlation between physiological properties shared between metal exposure and Huntington's disease. These include oxidative stress, cell stress, protein aggregation, and alterations in calcium signaling and energy metabolism. To test the correlations, they utilized several HD models in metal exposure paradigms. They first demonstrated that a mouse striatal cell line model of HD demonstrates variable cell survival responses to given metals. They note that mutant Huntingtin cells survive at similar rates over a range of concentrations in the vast majority of metals tested. However, mutant cells were less viable when exposed to cadmium and actually displayed a neuroprotective effect in the presence of manganese, without affecting the level of huntingtin protein.

The lab next capitalized on previous research to investigate the impact of manganese on established physiological processes. First, they demonstrated that HD mutant striatal cells have diminished phosphorylation of Akt, a cell stress signaling pathway associated with previous HD studies. They further show that these mutant cells have impaired accumulation of manganese, which may prevent its toxic intracellular effects. Finally they note that in an *in vivo* mouse model of HD, YAC128Q mice have a striatum-specific reduction of manganese uptake as compared to wild type mice. The neuroprotective effect of mutant HD on manganese exposure is quite surprising, and future experiments will target manganese uptake, export, and storage under the broad hypothesis that HD pathology is regulated in the context of both genetics and environment.

Original Research Article:
BB Williams, D Li, M Wegrzynowicz, BK Vadodaria, JG Anderson, **GF Kwakye**, M Aschner, KM Erikson, AB Bowman(2010). Disease-toxicant screen reveals a neuroprotective interaction between Huntington's disease and manganese exposure. *J. Neurochem*. **112** (1): 227-237.

Worth the 'EEfRT'? Role of motivation in rewarding tasks

Anhedonia is a subtype of the putative psychopathological enophenotypes in major depressive disorder (MDD), which characteristically represents an individual's aberrant motivation and reward responsivity. In order to objectively tap into the measures of reward motivation and test trait anhedonia, the authors in this study developed the Effort-Expenditure for Rewards Task (EEfRT or "effort"), a novel behavioral paradigm to explore effort based decision making in humans. The EEfRT task is a multi-trial game in which participants are given the opportunity on each trial to choose between two different task difficulty levels (hard or easy). They are required to complete the task with a specific number of button responses within a constrained period of time in order to obtain a monetary reward. Along with the EEfRT task, study participants self-reported measures of mood and trait anhedonia. Across multiple analyses, Treadway and colleagues found a significant inverse relationship between the anhedonia trait and a willingness to expend effort for rewards. From these results, the authors postulate that anhedonia is specifically associated with decreased motivation for reward. Additionally, the findings in this study enabled the authors to provide initial validation for the EEfRT behavioral paradigm as a laboratory based measure of reward motivation and effort based decision making in humans.

Original Research Article:
Treadway MT, **Buckholtz JW**, Schwartzman AN, Lambert WE, Zald DH (2009). Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS One*. 4(8):e6598.

IN BRIEF…

Exploring CAMKII associations with calcium L-type channels to regulate physiological changes in tissues

SA Abiria, RJ Colbran (2010). CaMKII associates with CaV1.2 L-type calcium channels via selected beta subunits to enhance regulatory phosphorylation. *J Neurochem*. **112** (1): 150-61.

Voltage activated L-type calcium channels (LTCCs) are known to generate Ca^{2+} signals important for numerous physiological process such as muscle contraction, neurotransmitters, neuronal plasticity and others. In particular the calcium/calmodulin dependant kinase II (CaMKII) protein has been shown to augment the Ca^{2+} signals in response to growth factors or hormones. Excessive $Ca_v1.2$LTCC activity can produce a variety of pathological symptoms including cardiac arrhythmias, multi-organ human genetic disorder and cases of parkinsons disease in animal models. While CAMKII facilitates LTCC activity physiologically, the molecular basis of CAMKII interactions and its modulation of LTCCs is yet to be understood. The authors of this paper transfected HEK293 cells from the forebrain of 7-8week old rats to explore the role of β subunits in targeting CAMKII to LTCC α1 subunits. They found that CAMKII co-immunoprecipitates with forebrain LTCCs that contain $Ca_v1.2$α1 and β1 or β2 subunits, but not LTCC complexes containing b4 subunits. These targeted mechanistic interactions between CAMKII and LTCCs will be crucial in providing insights into our understanding of physiological and pathological process in different tissues.