Presentation 11 – David Barber

Neurological Effects of Acute Uranium Exposure

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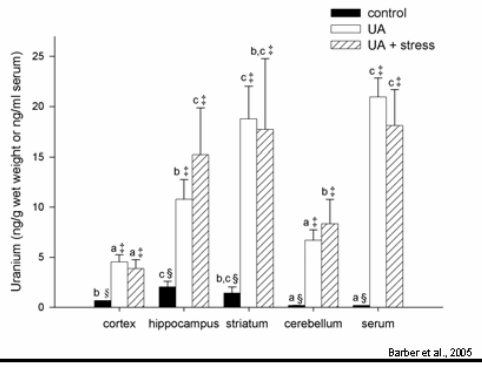
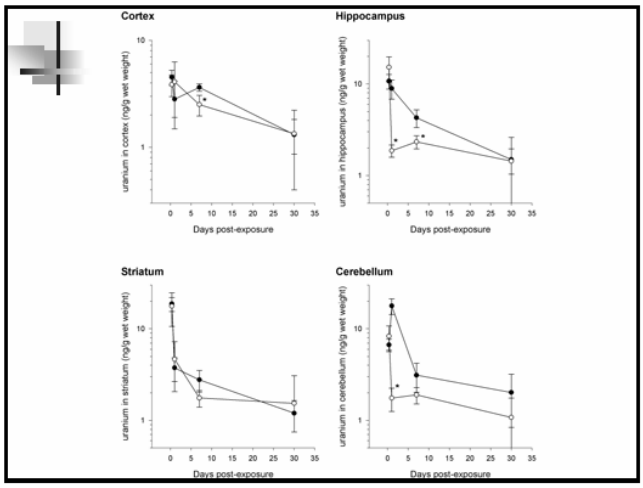
Background

- Many symptoms of GWI are potentially neurological in origin
- Two studies indicated that depleted uranium may have neurological effects
  - Pellmar *et al.* (1999) Hippocampal dysfunction in rats implanted with DU pellets
  - McDiarmid *et al.* (2000) Neurological deficits in exposed veterans with highest uranium excretion
- Chemical similarity of uranyl ion to lead and calcium
- Stress may alter the uptake of uranium

Goals of Study

- Several studies have shown that uranium enters the brain, but little information on kinetics of deposition and elimination or effects of DU on the nervous system
  - Examine the deposition and elimination of uranium in the brain
  - Determine if acute exposure to uranium produces neurological effects
  - Determine if prolonged exposure to uranium produces neurological effects
  - Determine if stress alters uranium deposition or neurological effects





- This study demonstrated that:
  - There are regional differences in brain uranium distribution
  - There are several phases of uranium elimination from the brain with the last phase being very long
  - Prior stress did not exacerbate the entry of uranium into the brain, if anything increased its elimination

Research Questions for Acute Toxicity Study

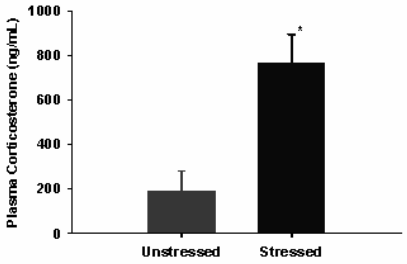
- It is clear that acute uranium exposure increases brain uranium levels, but are there observable effects on neuronal structure or function?
- Does the application of stress at the time of uranium exposure alter the effects of uranium on the nervous system?

Experimental Design

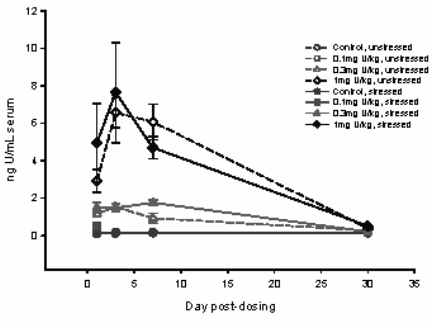
- Male Sprague Dawley rats
- Stress applied for 5 days prior to uranium exposure (restraint + swim)
- 0, 0.1, 0.3, and 1.0 mg uranium/kg administered as uranyl acetate by i.m. injection
- Tissue samples taken at 1, 3, 7,and 30 days for uranium levels, neurotransmitters, GSH, receptor number, and histopathology
  - Rats perfused with cold saline
  - Cerebral cortex, hippocampus, striatum, hypothalamus and cerebellum removed
  - Whole body perfusion fixation for histopathology

- FOB, motor activity, and passive avoidance performed on day 6, 13, 20, and 27
  - FOB evaluated behavioral and CNS excitability, autonomic effects, effects on muscle tone and equilibrium, effects on sensory systems, and effects on general physiology
  - Horizontal motor activity was determined by beam breaks in 2 minute segments over 30 minutes
  - Passive avoidance was used to evaluate memory. Rats trained prior to study initiation and examined weekly for retention of training.

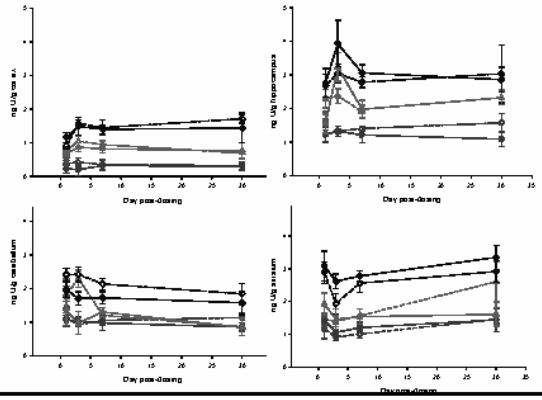
Stress



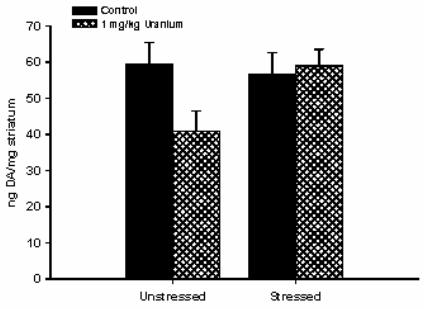
Serum uranium



Brain Uranium

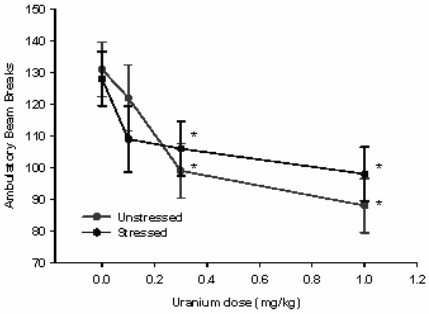


Striatal Dopamine on PD 3

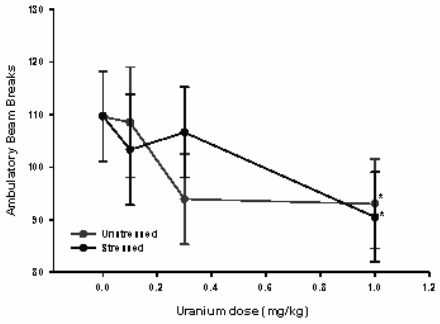


Uranium exposure decreases striatal dopamine in unstressed rats. Values are mean ± SD (N=5). * indicates values that are significantly different from control ($p<0.05$).

Ambulatory activity on PD 6



Ambulatory activity on PD 27

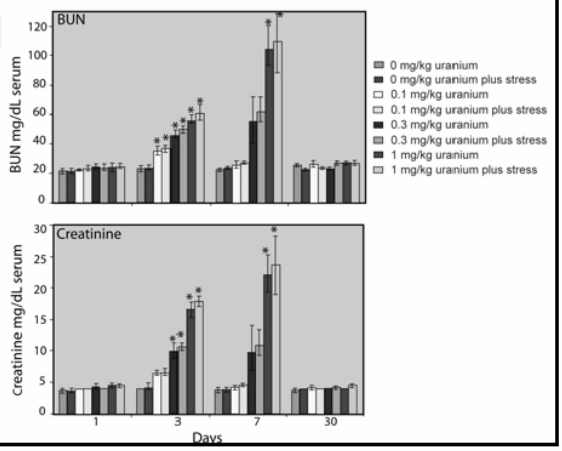


Uranium exposure decreases forelimb grip strength

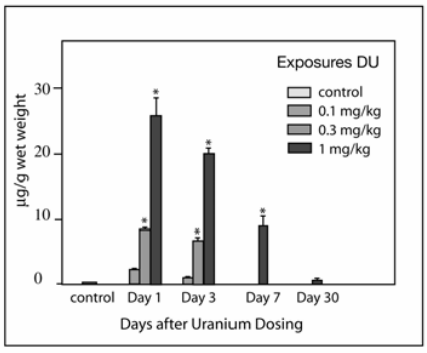
Day post-dosing	Uranium dose (mg/kg)	Forelimb Grip Strength (kg)	
		Unstressed	Stressed
6	0	1.83 ±0.04	1.81 ±0.05
	0.1	1.87 ±0.04	1.79 ±0.05
	0.3	1.79 ±0.03	1.76 ±0.03
	1.0	**1.70 ±0.07**	1.79 ±0.04
13	0	1.96 ±0.04	1.94 ±0.04
	0.1	2.01 ±0.02	2.05 ±0.03
	0.3	1.91 ±0.04	1.96 ±0.04
	1.0	**1.86 ±0.04**	1.93 ±0.03
20	0	2.01 ±0.06	1.98 ±0.05
	0.1	1.98 ±0.07	2.06 ±0.04
	0.3	1.90 ±0.04	1.94 ±0.05
	1.0	**1.87 ±0.06**	1.96 ±0.04
27	0	2.06 ±0.06	2.08 ±0.05
	0.1	2.08 ±0.03	2.09 ±0.07
	0.3	1.99 ±0.04	2.10 ±0.04
	1.0	**1.91 ±0.05**	1.99 ±0.04

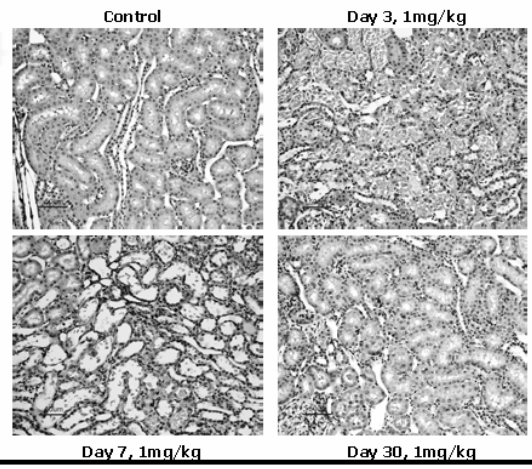
Other Results

- DU treatment initially produced decreased weight gain, but weights were equivalent to control by PD27
- DU and/or stress did not affect GABA, serotonin, norepinephrine, or glutathione content in striatum, hippocampus, cortex, or cerebellum
- DU did not affect performance in the passive avoidance assay, or indicators of CNS excitability, autonomic activity, equilibrium, or sensory perception
- No histopathological lesions in the CNS were visible on H&E stained sections
- All doses of DU produced some degree of renal injury and uremia



Kidney uranium





Summary

- A single intramuscular injection of uranyl acetate increased brain uranium for at least 30 days. Hippocampus and striatum accumulated higher uranium levels than cortex and cerebellum.
- A single exposure to uranyl acetate is capable of producing neurological effects that last for at least 27 days after exposure
- Stress at the time of uranium exposure had little effect on uranium levels, but did alter some behavioral and neurochemical parameters
  - Dose dependent decreases in ambulatory activity were observed. These effects were not significantly altered by prior stress.
  - A transient decrease in striatal dopamine was observed. This was ameliorated by prior stress
  - Small dose dependent decreases in forelimb grip strength were observed. These were ameliorated by prior stress.

- All doses produced some degree of uremia. It is difficult to separate direct neurological effects of uranium from secondary effects due to uremia.
- The timing, duration, and effect of stress suggest that effect on dopamine and forelimb grip strength may be direct effects of uranium.

Future Studies

- We are completing assays of D2 receptors in striatum, nACh receptor numbers in cortex and NMDA receptors in hippocampus.
- We are currently conducting a 6 month study utilizing implanted uranium and tantalum pellets (Pellmar et al., 1999) with stress applied throughout study.

Acknowledgements

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