Presentation 5 – Marina Morris

Low Level Chemical Toxicity
Study of Autonomic Neural Balance

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VA tests remedies for Gulf illness

Ailments may be linked to nerve gas antidote
Experimental Goals

- Phase 1: Stress/Chemical Interactions
  - *How does stress alter the body’s ability to resist chemical challenges?*
  - *Studies of pyridostigmine/stress interactions: focus on autonomic neural function*

Studies of Autonomic Balance
Integrative Cardiovascular Laboratory
Telemetric Recording of Blood Pressure in Two Mice Strains
What is Spectral Analysis?

- A statistical method for characterization of parameters of variability. Variation over time is considered variance. Power spectra of variability are composed of two oscillatory components; low frequency (LF: 0.1-1 Hz) and high frequency (HF: 1-5.0 Hz).

- The components are associated with autonomic balance. For HR and BP variability, LF is related to sympathetic modulation, whereas, for PI variability the HF is related to vagal modulation of the sinus node.

Signal Analysis
Clinical Relevance of Heart Rate Variability (HRV)

- HRV variability in chronic heart failure: Target for therapy? Sueta, 2003
- Decreased HRV variability is associated with increased mortality after acute myocardial infarction. Kleiger et al., 1987
- HRV strongly predicts cardiac death in heart failure patients. LaRovere et al., 2003

Reduced Heart Rate Variability Associated with Sudden Cardiac Death
Stress and Autonomic Regulation

Blood Pressure and Heart Rate Effects of Chronic PB & Stress

PROTOCOL
1. Three Days Duration
2. PB – 10 mg/kg/day
3. Shaker stress
   5 min, 90 times/day
Use of AChE Inhibitors in the Clinic

- Cholinergic stimulation with pyridostigmine reduces ventricular arrhythmias and enhances heart rate variability in heart failure. Behling et al., 2003
- Cholinergic stimulation with pyridostigmine reduces the QTc interval in coronary artery disease. Castro et al., 2003
Experimental Goals

♦ Phase 2: Low Level Sarin Exposure
  ▪ Genomic and Proteomic Expression
  ▪ Autonomic Neural Function
  ▪ Neurobehavioral and Cholinergic Function

Autonomic Cardiovascular Effects of Low Dose Sarin

♦ Radiotelemetry (5000Hz)
♦ Sarin sc (8 µg/kg)
♦ Spectral analysis - autoregressive method
♦ Blood and brain AChE
Low Dose Sarin
Brain and Blood Cholinesterase

![Graph showing ChE Activity (nmol/min/ug) for Control and Sarin groups.]

Low Dose Sarin
Blood Pressure and Heart Rate

![Graphs showing Mean Arterial Pressure and Heart Rate over time.]

Low Dose Sarin: Acute Increase in Heart Rate Variance

Acute Changes in Blood Pressure and Heart Rate Variance
Serendipity: The gift of finding valuable things not sought for

- **Action:** Your graduate student leaves the sarin treated mice in the animal facility for an extended vacation.

- **Outcome:** Cardiovascular monitoring shows that sarin produced delayed changes in heart rate variance, associated with cardiac dysfunction.

### Delayed Effect of Sarin on PI Variance and Frequency Domains

![Graph showing the delayed effect of sarin on PI Variance and Frequency Domains.](image-url)
Sarin on Blood Pressure Variance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Variance (mmHg²)</th>
<th>Low Freq (mmHg²)</th>
<th>High Freq (mmHg²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>13 ± 2</td>
<td>9 ± 2</td>
<td>3 ± 0.3</td>
</tr>
<tr>
<td>Sarin Acute</td>
<td>13 ± 3</td>
<td>9 ± 3</td>
<td>3 ± 1</td>
</tr>
<tr>
<td>Sarin Delayed</td>
<td>14 ± 2</td>
<td>10 ± 3</td>
<td>3 ± 1</td>
</tr>
</tbody>
</table>

Effect of Low Dose Sarin on Brainstem Catecholamine Systems
Low Dose Sarin Produces Delayed Changes in Brainstem Amine Function

Blunted Circadian Variation in Autonomic Regulation of Sinus Node Function in Veterans with Gulf War Syndrome

Robert W. Haley, MD, Wanpen Vongpatanasin, MD, Gil I. Wolfe, MD, Wilson W. Bryan, MD, Roseanne Armitage, PhD, Robert F. Hoffmann, PhD, Frederick Petty, PhD, MD, Timothy S. Callahan, PhD, Elizabeth Chanvivara, RN, William E. Shell, MD, W. Wesley Marshall, MD, Ronald G. Victor, MD
Conclusions

Sarin has effects on the brain and cardiovascular system at doses that cause no detectable clinical symptoms. These studies document the possible public health problems associated with low dose, non-symptomatic exposure to sarin.