Lead Neurotoxicity

Current Status and New Approaches

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Sources of Lead Exposure

- Pb-based paint in older homes/buildings
- Drinking water contamination from Pb compounds in plumbing
- Urban soil and dust

Disposition of Lead

- Absorption primarily by GI tract and lungs
  - GI absorption variable: highest in children
  - Ca, Zn, Fe compete with Pb for GI absorption
- Redistribution from liver and kidney mostly to bones, teeth and hair
  - eventually almost all in bone - SLOW turnover
  - circulating Pb in red blood cells →*recent exposure*
- Bone deposition → slow urinary excretion

Lead Levels in Population

- average blood lead levels in U.S. = 3 ug/100 ml
- levels in children (1-2 yrs) = 4 ug/100 ml
- % children with blood leads $\geq$ 10 ug/100 ml = 6-7% (1.7 million)
- blood levels indicating need for medical attention: 10 ug/100 ml (children), 25 ug/100 ml (adults)

CNS Toxicity From Lead

- children are population at greatest risk
  - elevated GI absorption of Pb
  - incompletely developed blood-brain barrier
- lead encephalopathy: a medical emergency
  - high proportion of deaths, irreversible neurological signs
- chronic exposure to low levels impairs learning ability

Lead and Cognitive Dysfunction in Children - Symptoms

- Increased distractibility, short attention span
- Impulsivity, non-persistence
- Inability to follow sequences of directions
- Inappropriate approach to problems
- Robust deficits in learned skills

Lead and Cognitive Dysfunction in Children

- Decreased developmental scores in infants
  - prenatal lead level and developmental status at 6-18 months of age
- Meta-analysis: 0.25 IQ point decrease per ug/deciliter increase in blood lead
- Decrements in school performance and measures of attention
  - persistent problems into young adulthood

Need for Animal Research on Low-Level Lead Exposure

- to determine mechanisms of neuronal dysfunction
- to elucidate the cognitive-impairing mechanism
- to develop improved therapy

Animal Studies - Behavior

- Greatest similarities involve complex processes such as cognition and learning
- Lowest levels of exposure at which effects have been observed are similar
  - children: $\leq$ 10 µg Pb/dl
  - primates: < 15 µg Pb/dl
  - rodents: ~ 10 µg Pb/dl

Pb Neurotoxicity – Research Foci

- Neurotransmitter release – Glu, DA, ACh
- NMDA receptor function – basis for learning impairment?
- Neurogenesis, neuronal growth/development
- Synaptic plasticity – as a correlate of learning

Pb Toxicity – Acute *In Vitro* Exposure

- Pb^{+2} mimics or substitutes for the actions of Ca^{+2} in many cellular processes
- Pb^{+2} is a strong Ca^{+2}-mimetic in enhancing spontaneous transmitter release
- Pb^{+2} also inhibits evoked transmitter release

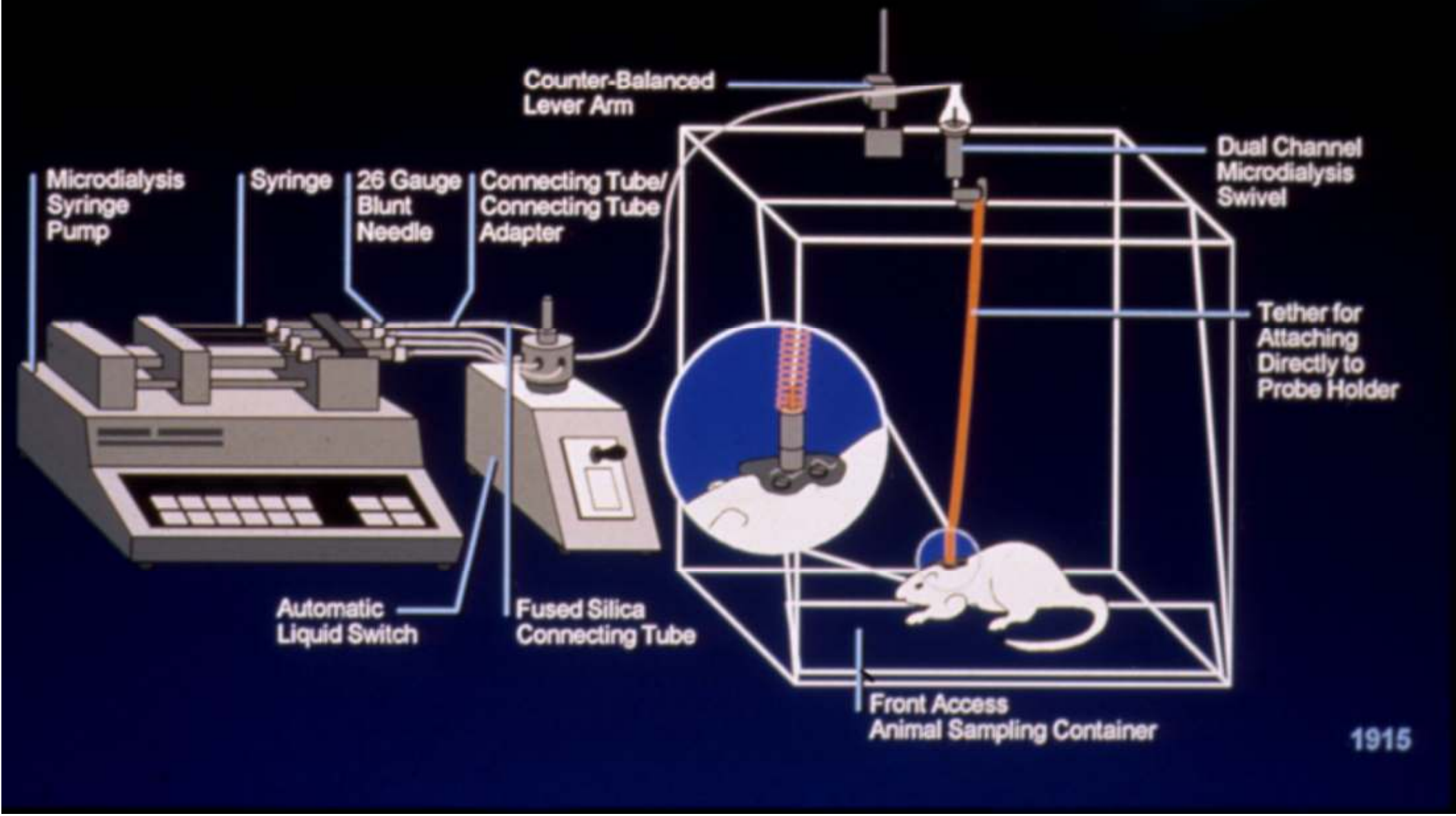
Problem

Well established cellular actions of Pb^{+2} could not be readily linked to the behavioral action of Pb in humans or animal models

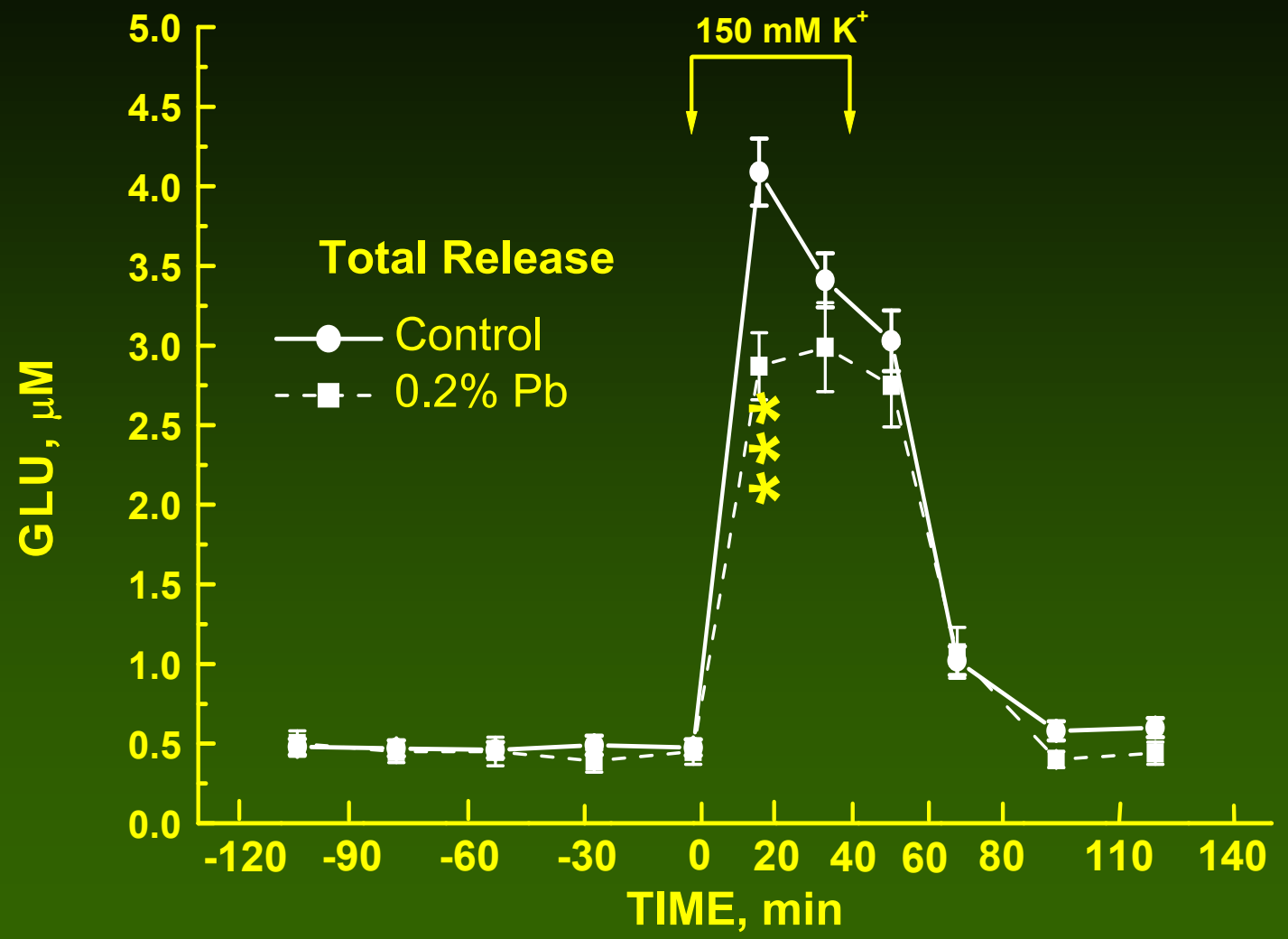
In Vivo Microdialysis To Evaluate Transmitter Release

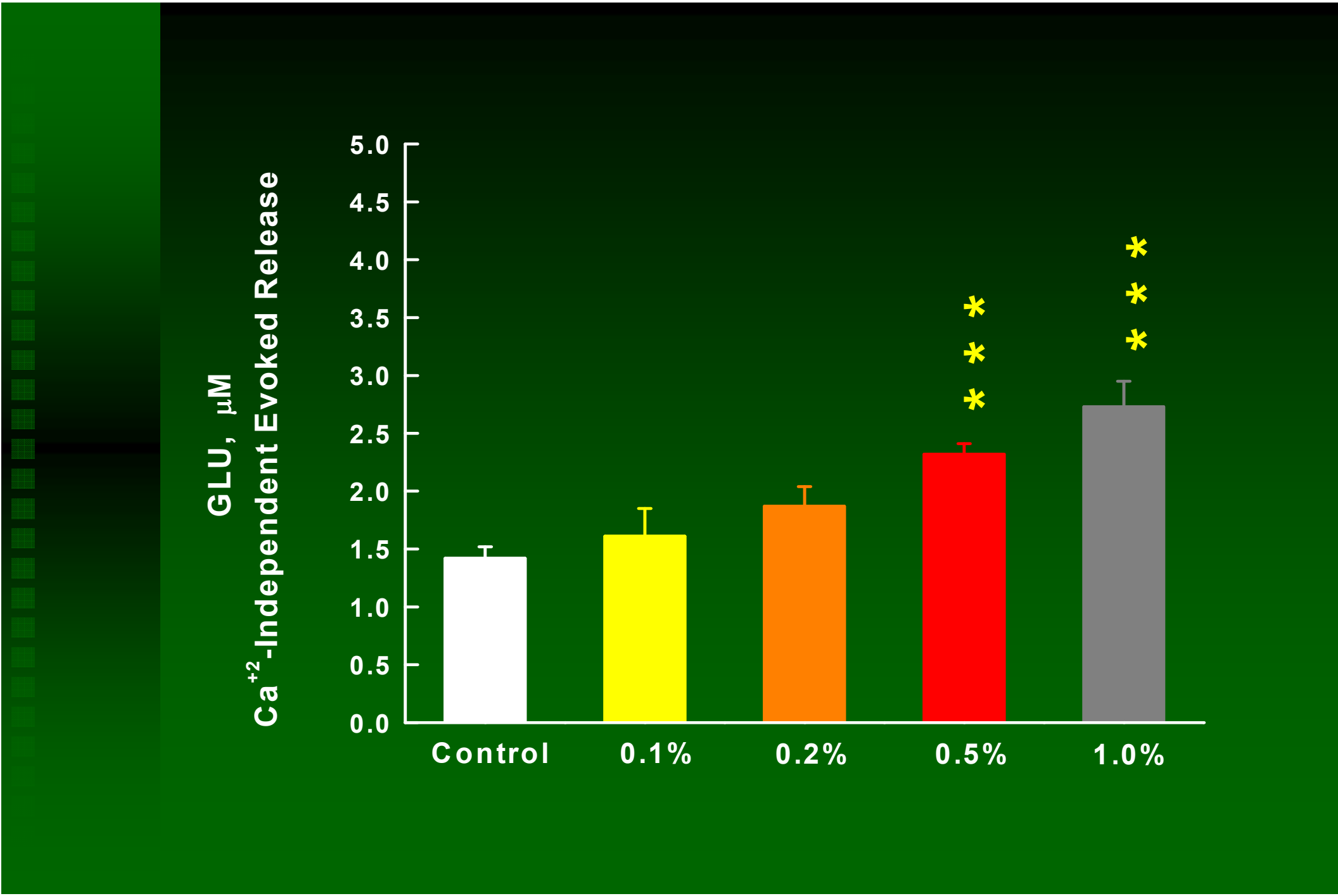
In Vivo Long Term Potentiation Model of Learning and Memory

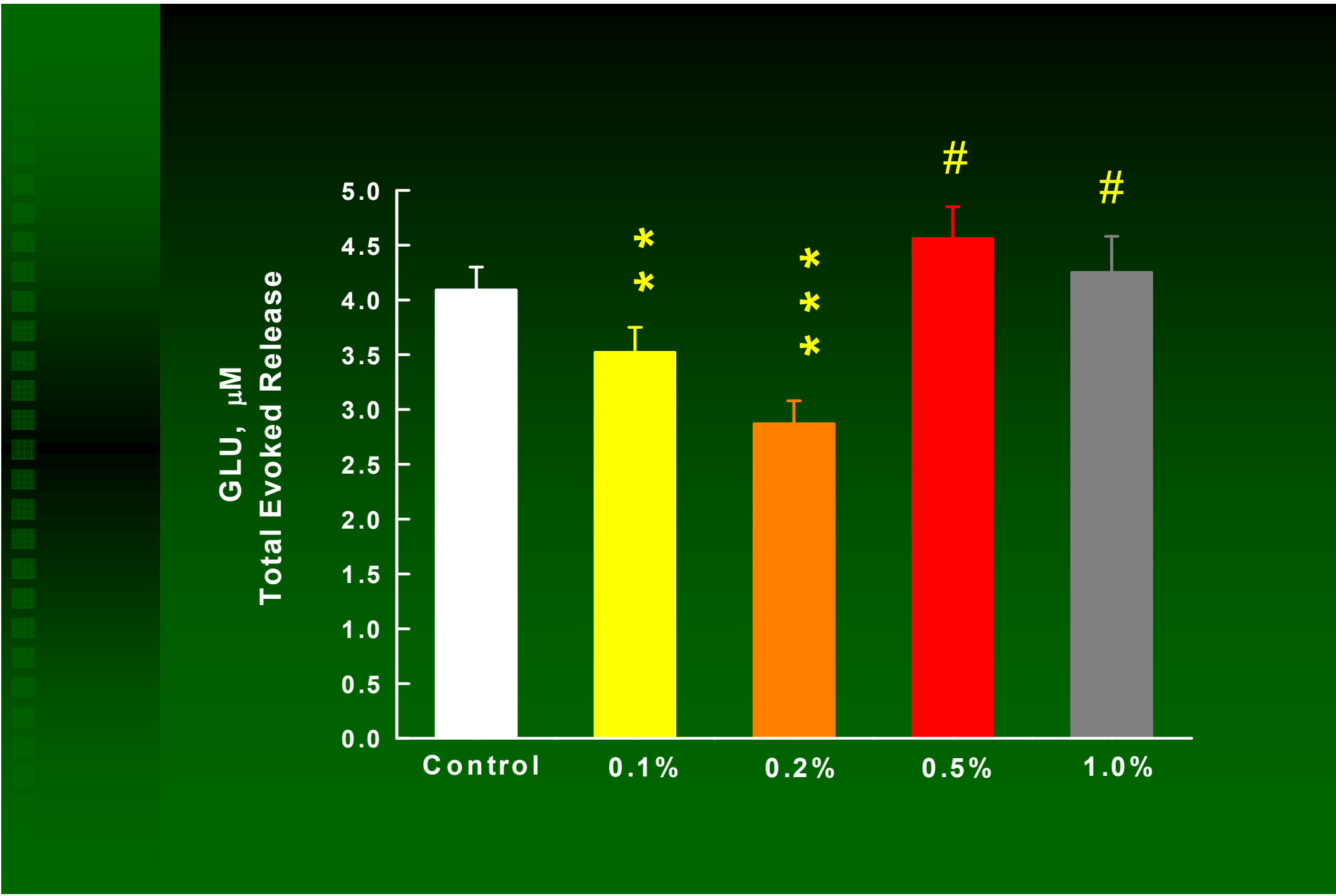
Freely Moving Animal Setup



1915

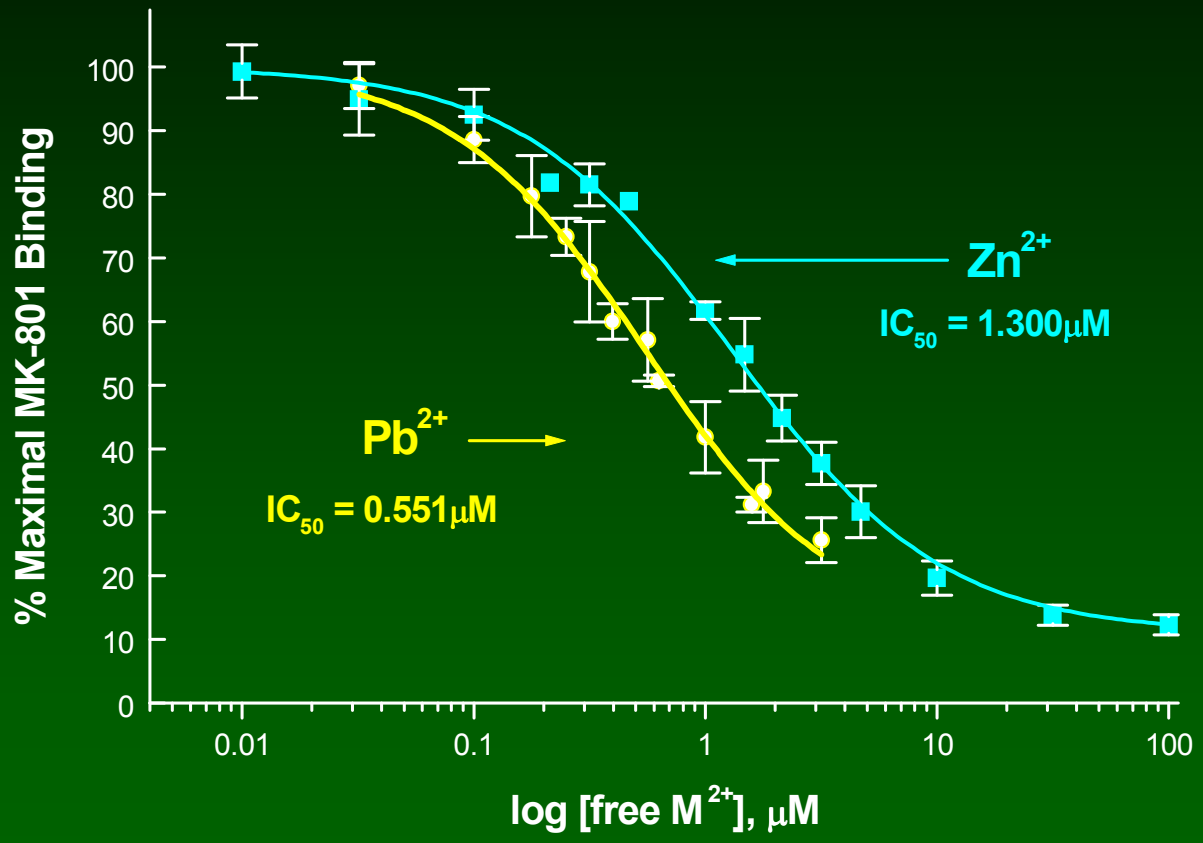

150 mM K+
Total Release
Control
0.2% Pb
GLU, μM
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-120
-90
-60
-30
0
20
40
60
80
110
140
TIME, min
***

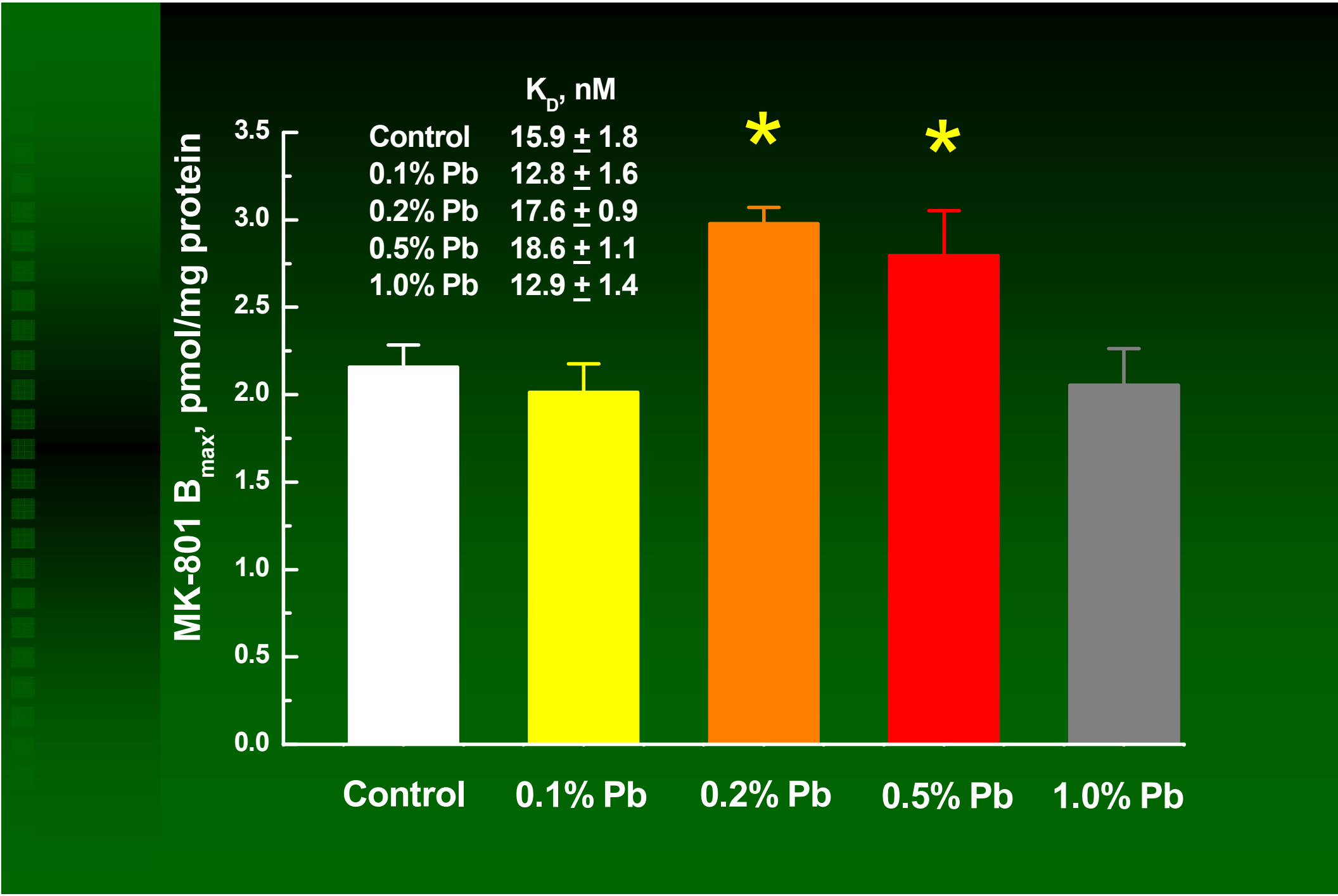

GLU, μM
Ca+2-Independent Evoked Release
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Control
0.1%
0.2%
0.5%
1.0%
*
*
*
*
*


GLU, μM
Total Evoked Release
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
*
*
*
#
#
Control
0.1%
0.2%
0.5%
1.0%

Pb Neurotoxicity – Glutamate Release

- Pb^{+2} mimics or substitutes for the actions of Ca^{+2} in many cellular processes
  - most have no defined link to learning or LTP
- Pb^{+2} a strong Ca^{+2}-mimetic in supporting glutamate release
- Pb^{+2} also inhibits evoked glutamate release


% Maximal MK-801 Binding
100
90
80
70
60
50
40
30
20
10
0
0.01
0.1
1
10
100
log [free M2+], μM
Zn2+
IC50 = 1.300μM
Pb2+
IC50 = 0.551μM


K_D, nM
Control 15.9 ± 1.8
0.1% Pb 12.8 ± 1.6
0.2% Pb 17.6 ± 0.9
0.5% Pb 18.6 ± 1.1
1.0% Pb 12.9 ± 1.4
*
*
MK-801 B_{max}, pmol/mg protein
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Control
0.1% Pb
0.2% Pb
0.5% Pb
1.0% Pb

Pb Neurotoxicity – NMDA Receptors

- No apparent direct Pb^{+2} inhibition at environmental exposures
- Chronic exposure increases receptor density
- Functional import of exposure-induced changes in receptor subunit composition not established

Conclusion: NMDA receptors not primary basis of cognitive impairment

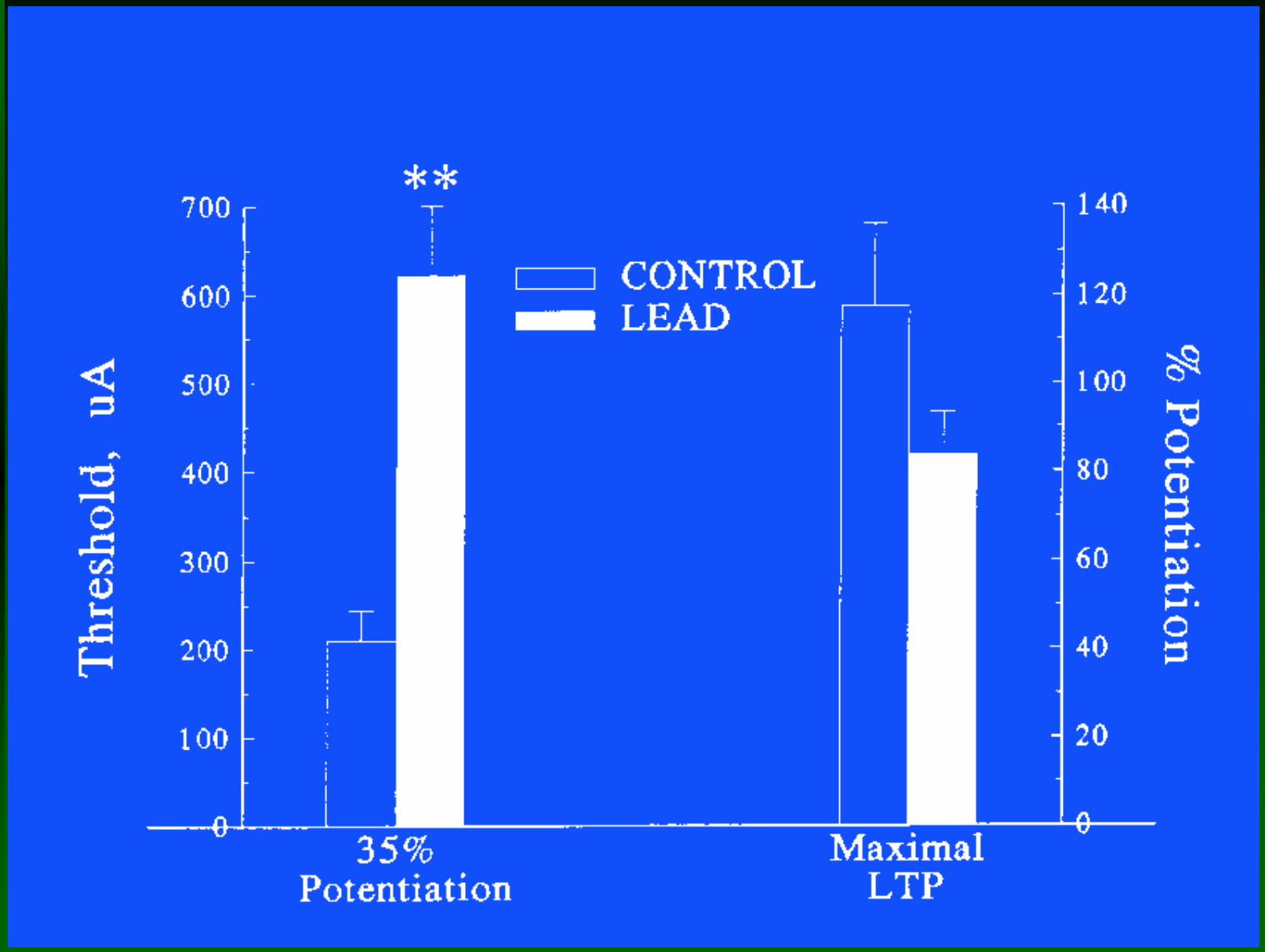
Pb Neurotoxicity – Neurogenesis, Neuronal Development

- Reduced capacity for hippocampal neurogenesis
- Reduced neuronal volume density in primary visual cortical areas
- Reduced number of axonal arborizations
- Dose-related reduction in cortical field area

Conclusion: Environmental lead exposure inhibits neuronal development

Animal Studies - Neurophysiological Correlates

- Model needed that is closely related to behavior: long-term potentiation (LTP)
  - a physiological model of information storage at the level of the synapse
- LTP thought to utilize same synaptic mechanisms as the learning process

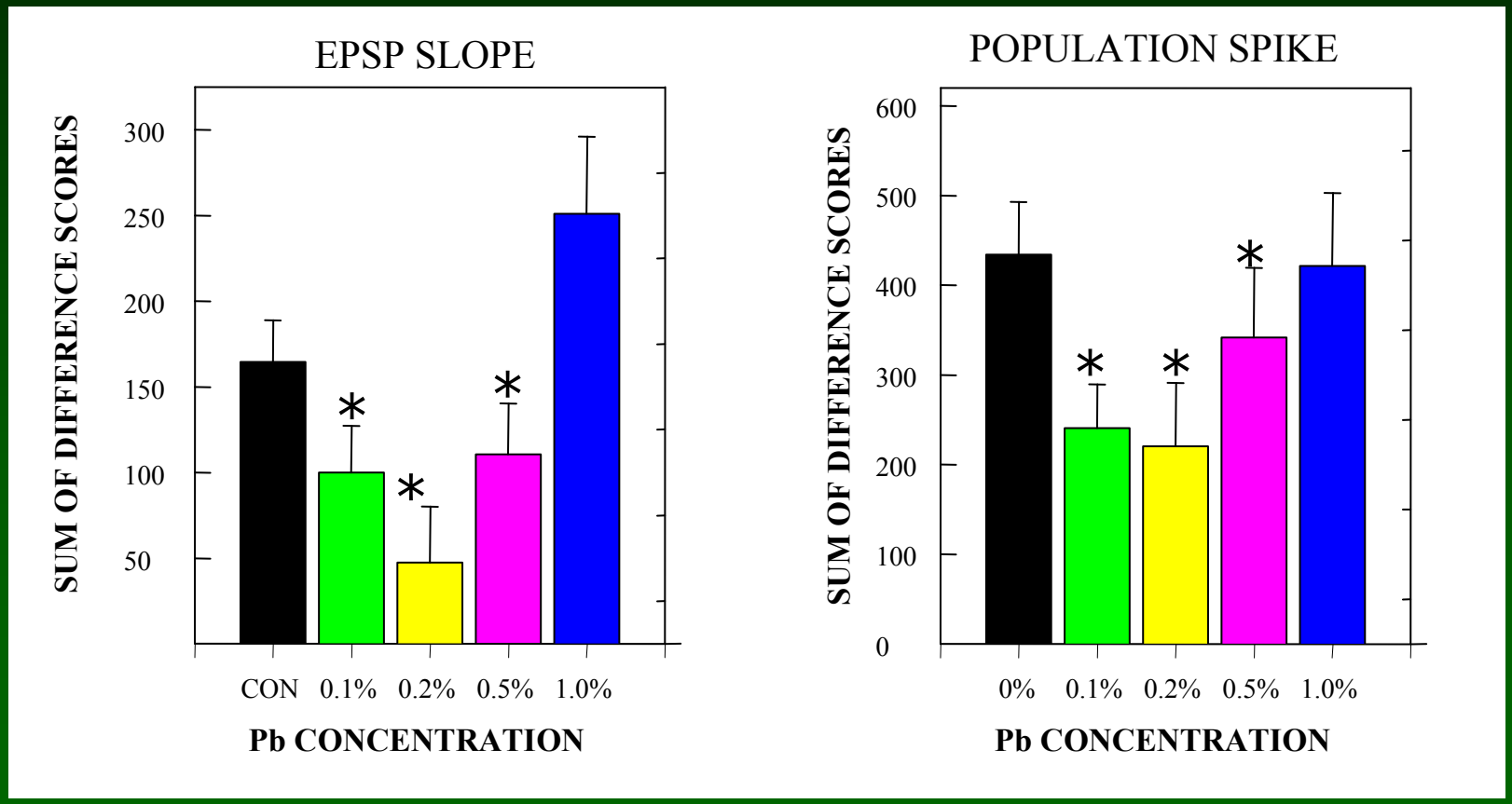

**
700
600
500
400
300
200
100
0
Threshold, uA
CONTROL
LEAD
140
120
100
80
60
40
20
0
% Potentiation
35%
Potentiation
Maximal
LTP

Lead Exposure and LTP

Chronic lead:

- Does not alter normal synaptic physiology
- Impairs LTP at cortical, hippocampal (CA1, dentate) sites
- Increases the threshold for LTP induction, reduces the magnitude of potentiation, and shortens duration

Biphasic Dose-Response Profile in LTP



Chelating Agents for Lead

- $CaNa_2EDTA$ - chelates water-soluble, readily excreted
  - administered parenterally for 3-5 days
  - adverse reactions common, renal toxicity most serious
- DMSA - orally effective, less toxic
  - plasma levels of other essential metals unchanged
- Dimercaprol - used in combination with EDTA for severe lead poisoning
  - parenteral administration, adverse reactions common
- patient follow-up required

Guidelines for Management of Lead Toxicity

- most important factor: reduce exposure

- ≤ 24 ug/100 ml: educational/nutritional intervention, environmental remediation
- 25-44 ug/100 ml: EDTA mobilization test or DMSA therapy
- 45-69 ug/100 ml: chelation therapy (EDTA or DMSA
- ≥ 70 ug/100 ml: EDTA plus dimercaprol (medical emergency)

Chelation Efficacy and Cognitive Impairment – Clinical Trial

- 780 children, PbB: 20-44 µg/dl
- 12-33 months, > 75% black
- Randomized, placebo-controlled, double-blind
- ≤ three 26-day courses of DMSA
- Followup behavioral testing for 36 months

- Source: Rogan *et al.*, *New Engl J Med* **344**, 1421 (2001)

Chelation Efficacy and Cognitive Impairment - Results

- PbB values decreased ~ 5 μg/dl over 6 months
- 36 months followup: IQ scores, behavioral ratings, neuropsychological assessments were not improved
- Source: Rogan *et al.*, *New Engl J Med* **344**, 1421 (2001)

Chelation Efficacy and Cognitive Impairment - Conclusions

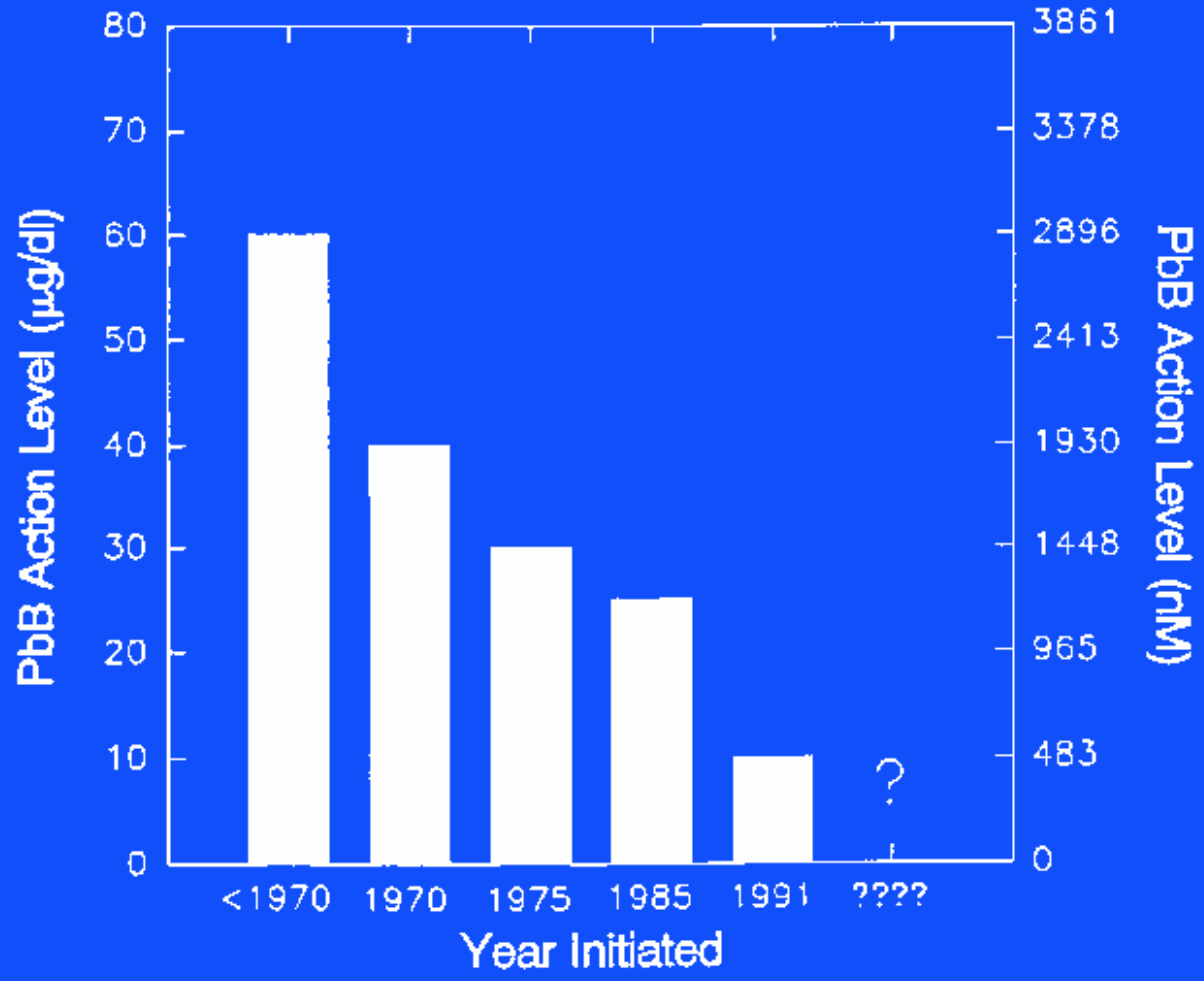
1. Chelation does not reverse cognitive impairment in exposed children.
2. Chelation valuable to treat Pb poisoning to decrease lethality, provide symptomatic relief
3. Emphasis in addressing Pb neurotoxicity is on prevention of exposure.

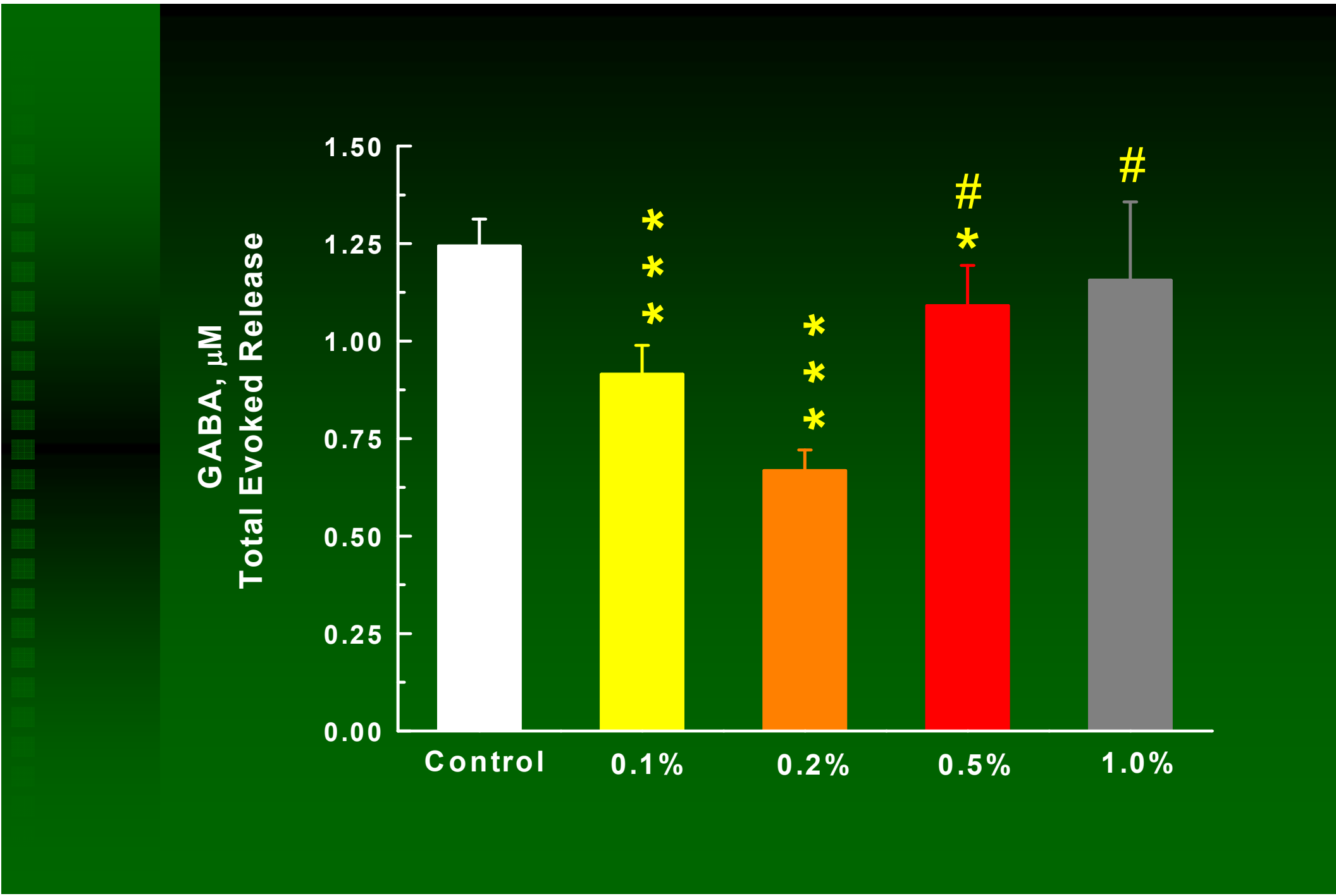
The Future for Pb Neurotoxicity?

- Further development of chelation therapy unlikely
  - Challenge: improving affinity and selectivity of chelating agent for Pb^{+2}
- Remediation of contaminated environments – not after the fact

The Future for Pb Neurotoxicity?

- New approaches: treatments for the neuronal effects of exposure
  - Environmental enrichment, physical exercise
  - Development of neurotrophin pharmacology
  - Targeted delivery of neurotrophins – NGF, BDNF


PbB Action Level (µg/dl)
80
70
60
50
40
30
20
10
0
3861
3378
2896
2413
1930
1448
965
483
0
PbB Action Level (nM)
?
<1970
1970
1975
1985
1991
????
Year Initiated


GABA, µM
Total Evoked Release
1.50
1.25
1.00
0.75
0.50
0.25
0.00
***
***
**
#
#
Control
0.1%
0.2%
0.5%
1.0%

Microdialysis Protocol