Name:_____

UNIVERSITY OF TORONTO
Faculty of Arts and Science

APRIL 2014 EXAMINATIONS

PSL-444Y, JNR-144Y, and PSL-1446H

Duration - 3 hours

No Aids Allowed

Total Marks: 140

Total pages: 15

Dr. Bill Ju (20 marks total)

A recent manuscript published in 2013 by Granger, A.J., Shi, Y., Lu, W., Cerpas, M. & Nicoll, R.A. entitled *"LTP requires a reserve pool of glutamate receptors independent of subunit type"* (Nature 493:495-501) reports that intracellular glutamate receptor subunits are capable of trafficking to the cell surface but that the types of subunits are not important for the production of LTP (long term potentiation). One major criticism of this paper is that they did not use any imaging or biochemical tests to show that there was an increased synaptic expression of specific receptors.

1. Based on what you have learned in class, provide one method that Granger et al., could use to epitope tag AMPA receptor subunits.

2. Provide a rationale for which glutamate receptor subunits they would likely want to investigate in the LTP phenomenon.

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Dr. Bill Ju (Continued)

3. Provide specific experimental details of how they could visualize movement from intracellular to synaptic compartments using the system you have outlined above.

4. What are advantages/disadvantages would be associated with your method.

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Dr. James Eubanks (20 marks total)

In class we discussed the molecular alterations that cause the synaptic disorders of Fragile X syndrome, Coffin-Lowry syndrome, Rubinstein-Taybi syndrome, and Rett syndrome. Each of these conditions is associated with severe cognitive impairment, and hippocampal synapses in mouse models for each condition possess significantly diminished levels of synaptic plasticity.

Part A: Please name the primary mutated genes responsible for the majority of Fragile X syndrome, Coffin-Lowry syndrome, Rubinstein-Taybi syndrome, and Rett syndrome cases. (2 marks)

Part B: Please name what is believed to be the primary function associated with each of the protein products for each of these genes. (2 marks)

Part C: In each of these conditions, the causal mutation is associated with a defect in normal developmental synaptic selection and/or strengthening/maturation. Please select ONE of the four conditions, and discuss how the following alterations arise from the mutated protein you select: (1) activity-dependent local signaling, (2) altered epigenetic balance within the nucleus, and (3) altered profiles of gene expression. Finally, (4) describe how these changes lead to the synaptic deficits of the condition you select. For each answer, clearly state how the causal mutated gene product factors into your proposed mechanism. (8 marks).

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Dr. James Eubanks (Continued)

Part D: Select one of the four conditions, ***but a different one from what you chose in Part C***. Given what you know about the causal gene and the neurological impairments seen in the condition, propose a strategy that could potentially be used to treat the condition in patients (e.g., ***do not*** employ experimental mouse models). Then, identify potential limitations or problems that could be encountered with the strategy you propose. Note: there are no current treatments for any of these conditions, so your answer must incorporate the rationale for why you think your strategy *could* be beneficial. (8 marks).

Dr. James Eubanks (10 marks total)

Please answer ONE of the following questions.

1. Discuss how progeria conditions have influenced hypotheses on aging mechanisms.
2. Assuming the mitochondrial hypothesis of aging has merit, discuss ***one*** drug strategy, and ***one*** lifestyle strategy, that could be attempted to extend lifespan and improve quality of life in old age.
3. Discuss the Telomeric Theory of Aging. Include evidence in support of this theory and also comment on some of its limitations.
4. Discuss why the caloric-restriction diet has gained considerable attention recently as a potential longevity-enhancing mechanism.
5. The family of Sirtuins has been hypothesized to be mediators of longevity. Discuss the evidence in support of their role as anti-aging factors.

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Dr. Linda Mills (10 marks total)

Discuss **ONE** of the Following Questions Only (in short essay format)

1. Thinking about what you have learned in the course this year, propose a hypothesis or strategy you could test in humans, or any model of choice, that is relevant to some aspect of brain aging. Tip: This is a broad question, so keep your focus narrow.

2. Calcium dyshomeostasis and mitochondria dysfunction are two theories implicated in brain aging. Discuss how these could be linked and comment on whether you think they are sufficient to explain brain aging.

3. Studies suggest that exercise can prevent/reverse age-related changes in animal models and in humans. Critically discuss this hypothesis and describe how you could test it. Assume unlimited financial resources.

4. What are the anatomical and functional correlates of normal brain aging in humans / rhesus macaque monkeys. Discuss the implications of findings that gene expression profiles differ in aging mouse/monkey/man.

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Dr. Tom Johnston (20 marks total)

Several drug strategies are currently being developed to treat Parkinson's disease.

Part A: List one example of a class of drug that is being developed to treat each of the following features: (1) the motor symptoms of Parkinson's disease; (2) the complications that arise from existing treatment strategies (e.g. dyskinesia); and (3) agents that slow or prevent the progression (i.e. underlying pathology) of Parkinson's disease. (4 Marks)

Part B: For the single example that you described above, give the name of a specific compound and describe its proposed mechanism of action. (16 Marks)

Dr. JoAnne McLaurin (20 Marks)

1. Match up disease and a potential treatment strategy. Choose only one treatment per disease (2 marks each, 10 total).

Multiple Sclerosis	Intravenous Immunoglobulins
Paraneoplastic Disorder	Antibody to Abeta peptide
Myasthenia Gravis	Plasma Exchange
Alzheimer's Disease	IL-3 treatment
Viral Infection of the brain	Immunosuppression

2. You cross an APP-overexpressing mouse with a mouse that is unable to produce reactive oxygen species. Choose one phenotype that would result from this cross (3 marks), and then provide the rationale for why this phenotype would be seen in the resulting mouse (7 marks). Transcribing charts from class will not be acceptable justification.

Dr. Peter Carlen (20 marks total)

You are given a drug with convulsant properties and have been asked to decide if its mechanism of action is via GABAergic inhibition or enhanced gap junctional coupling. Describe strategies to differentiate these 2 putative mechanisms using in vivo and in vitro experimentation. (20 Marks)

Dr. Charles Tator (10 Marks)

Answer ONE of following questions:

A) Describe the pathophysiology of acute spinal cord injury.
B) Describe strategies for promoting regeneration in the injured spinal cord.

Dr. James Eubanks (10 Marks)

Please answer each of the following questions.

a) Calcium ion influx through glutamate receptors is believed to initiate cell death pathways within the context of a focal ischemic stroke. List four (4) downstream consequences of immediate calcium influx overload that have been hypothesized to participate in cell death following the onset of cerebral ischemia. (2 marks)

b) There are two predominant components to a global ischemic stroke: the ischemic insult itself, and the reperfusion that occurs following resuscitation. Discuss key molecular events that are believed to contribute to the ***delayed*** degeneration of sensitive neurons that occur during the ischemic and reperfusion components (4 marks).

Dr. James Eubanks (continued)

c) The pharmaceutical industry has invested millions of dollars towards the development of glutamate receptor antagonists to treat focal ischemia. Do you believe this money was well spent? Discuss why or why not? (4 marks)

Extra Sheet If Needed – Please identify the question being addressed on this page at the top right.