Neurobiology of Respiration – CSB346H
Term Test
Test duration 90 minutes
This test is worth 25% of final grade
Total marks 98

Multiple Choice Questions (12 marks)

1) You are hiking down into a canyon and are breathing 30 times per minute with a tidal volume of 450 ml and a dead space volume of 135 ml. Your working tissues are consuming 570 ml of O_2 per minute and all of the O_2 inspired diffuses into your pulmonary capillaries. How many milliliters of O_2 do you acquire each minute and are you hypernic (i.e. hyperna), hyperventilating or hypoventilating?

A. 9.5L/minute; hyperventilating
B. 2L/minute; hyperpnic
C. 13.5L/minute; hypoventilating
D. 2L/minute; hyperventilating
E. 9.5L/minute; hyperpnic

2) What is the pre-Botzinger complex?

A. A group of cells located in the ventral respiratory group that are solely responsible for generating breathing movements in-vivo
B. A group of cells located in the dorsal respiratory group that generate breathing movements in-vivo
C. A group of neurons from the ventral respiratory group that only contain pacemaker neurons
D. A group of neurons from the pontine respiratory group that are rhythmically active and only expression NKR1
E. None of the above

3) What happens to breathing when DAMGO (micro-opioid agonist) is injected into the pre-BotC?

A. Breathing is not influenced by this intervention
B. Tidal volume is unaffected but respiratory frequency decreases
C. Hyperventilation occurs because breathing rate slows
D. Breathing stops completely
E. None of the above

4) Which of the following muscle groups contract during inspiration?

A. Diaphragm; external intercostals; gengioglossus

B. Internal intercostals; gengioglossus; tensor levator palatini
C. Tensor levator palatini; external intercostals; internal intercostals
D. Internal intercostals; abdominus rectus; tensor levator palatini
E. All of the above

5) Which respiratory motoneurons innervate the diaphragm, genioglossus and soft palate muscles, respectively?

A. Phrenic; trigeminal; nucleus ambiguus
B. Hypoglossal; trigeminal; phrenic
C. Phrenic; hypoglossal; trigeminal
D. Trigeminal; facial; hypoglossal
E. Hypoglossal; facial; phrenic

6) What happens to breathing when saporin conjugated with the neurokinin-1 receptor antibody is injected into the pre-BotC of a rat?

A. Breathing is normal immediately after the saporin injection
B. Breathing becomes irregular during sleep then during waking
C. Within the first 6 hours breathing is normal in waking but stops (i.e. apnea) only when the rat enters rapid eye movement (REM) sleep)
D. Breathing is irregular during non-rapid eye movement (NREM) sleep immediately after the saporin is injected
E. Both A and B

7) Which of the following statements concerning the O_2-dissociation curve is correct?

A. The O_2-dissociation curve illustrates the interaction between venous hemoglobin saturation and ambient PO_2
B. A rightward shift in the curve indicates that hemoglobin is more likely to bind with O2 at any given PO_2
C. A rightward shift in the curve can be caused by an increase in inspirited CO_2 concentration
D. A leftward shift in the curve indicates that hemoglobin is less likely to bind with O_2 at any given PO_2
E. A leftward shift in the curve can be caused by a decrease in venous pH

8) What happens to breathing when the drosophila allatostatin receptor is expressed int he pre-BotC of rats and allatostatin is applied?

A. Inspiratory amplitude decreases and respiratory rate increase
B. Inspiratory amplitude increases and respiratory rate increases
C. Inspiratory amplitude increases and respiratory rate increases
D. Inspiratory amplitude decreases and respiratory rate decreases

E. None of the above

9. Hyperventilation ___________ the partial pressure of CO_2 in the ___________ blood supply to the brain and during sleep this can cause ______________.

A. Increases; arterial; dyspnea
B. Reduces; arterial; apnea
C. Increase; venous; bradycardia
D. Reduces; arterial; hypernpnea
E. Reduces; venous; apnea

10. Genetic insertion of allatostatin receptors into the pre-BotC is an effective method for modulating the normal activity respiratory neurons in this region. What happens to neurons when allatostatin is applied into the pre-BotC?

A. It closes potassium channels and increases cell activity
B. It opens potassium channels and hyperpolarizes neurons
C. It opens chloride channels and kills neurons
D. It closes potassium channels and depolarizes neurons
E. It closes chloride channels and hyperpolarizes neurons

11. Application of depolarizing currents into inspiratory neurons without pacemaker potentials causes them to ___; whereas this same current injection into inspiratory neurons with pacemaker potentials causes them to ____.

A. Depolarize and fire bursts of action potentials; hyperpolarize and fire action potentials randomly
B. Hyperpolarize and stop firing action potentials randomly; depolarize and fire bursts of action potentials that are correlated with inspiration
C. Depolarize and stop firing action potentials; depolarize and fire bursts of action potentials
D. Hyperpolarize and stop firing action potentials; depolarize and stop firing action potentials

12. The figure below illustrates how the activity of the neurons in the _____ of the rostral medulla changes across the respiratory cycle in an in-vitro medullary preparation. What is the time point (relative to the onset of phrenic nerve discharge) at which neurons in this region first become clearly active?

A. Pre-Botzinger complex; -400ms
B. Ventral respiratory group; -200ms
C. Para-facial respiratory group; -200ms
D. Retrotrapezoid nucleus; -100ms
E. Pre-Botzinger complex; -100ms

True or false questions (16 marks)
True = A and false = B

13) The smallest respiratory gas exchange unit is the alveolar Type I cell

14) The retrotrapezoid nucleus (also called the parafacial nucleus) is located dorsal and ventral to the pre-BotC.

15) Peripheral chemoreceptors also called carotid bodies are located at the bifurcation of the internal and external carotid veins

16) Cells in the retrotrapezoid nucleus fire action potentials during the expiratory phase of the respiratory cycle.

17) Synaptic inhibition is involved in generating respiratory rhythm in neonatal rat brains.

18) Pacemaker potentials are essential for generating respiratory rhythm in the transverse slice in-vitro.

19) Gengioglossus and external intercostals muscles are normally activated during active expiration.

20) Carotid bodies are more sensitive to low levels of both CO_2 and O_2.

21) There are both pacemaker and non-pacemaker neurons located in the ventral respiratory group.

22) Central chemoreceptors are located on the ventral surface of the cervical spinal cord.

23) Applying bicuculline and strychnine, GABA and glycine receptor antagonists, to the pre-BotC in-vivo stops breathing

24) The ventral respiratory group containe din the lef thald of the brainstem generates a breathing rhythm that is dependent of the ventral respiratory group contained in the right side of the brainstem.

25) The retrotrapezoid nucleus is not contained within the transverse medullary slice that generates respiratory rhythm in-vitro.

26) The pacemaker, network and hybrid models are hypothetical ideas that are used to explain the fundamental mechanisms by which breathing is generated.

27) During active ventilation, such as during vigorous exercise, the activity of internal intercostals muscles increases during exhalation and decrease during inhalation.

Short Answer Questions (22 marks)
Use no more than 8 words to answer each of the following questions.

1) Name 2 structures that make up the blood-gas interface. (2 marks)
Alveolar epithelium
Capillary endothelium

2) Name the 3 classical chemosensitive zones and the people who discovered them. (3 marks)
M – discovered by Mitchell
S – discovered by Schlafke
L – discovered by Loescke

3) Is the dorsal respiratory group located rostral or caudal to the pontine respiratory group? (2 marks)
Caudal

4) Name 2 separate brain regions that are sensitive to CO_2 (pH) levels. (2 marks)

5) Name 4 motor behaviors, other than breathing, that are controlled by rhythm generators. (4 marks)
Locotion
Chewing
Swallowing
Eye movements

6) Name the 3 ions responsible for generating pacemaker potentials. (3 marks)
K^+
Na^+
Ca^{2+}

7) Name 3 separate proteins that are sensitive to changes in pH. (2 marks)
Gap junctions
TASK channels
K^+ channels

8) Identify 2 separate effects that cigarette smoke has on gas exchange in the lungs. (2 marks)
It destroys the alveoli (reduces surface area gas exchange) and destroys the capillaries (reduce O_2 transport)

9) Which nerve relays information from the peripheral chemoreceptors to the central nervous system? In which brainstem nucleus does this nerve terminate? (2 marks)
The nerve is the glossopharyngeal nerve afferent and it terminates in the nucleus of solitary tract.

Short Answer Questions (48 marks)
Use no more than 12 sentences to answer each of the following questions.

1) (i) Draw a block diagram illustrating the neural pathways by which respiratory rhythm is transmitted from the medulla to the tongue. Identify 2 possible brainstem areas responsible for rhythm generation and indicate whether these areas communicate with each other. Show the motor nuclei that these areas project to and indicate which muscle in the tongue is affected. Make sure all parts of the figure are clearly labelled (5 marks).
Medulla contains

- **Ventral respiratory group: Pre-BotC (contained w/in VRG) → Motor pool → Premotor neuron → Cranial nerve XII (hypoglossal nerve) → Genioglossus muscle in tongue**
- **Dorsal respiratory group**

(ii) Write (in sentence form) at what point this tongue muscle is active during the respiratory cycle and how reductions in this muscle's activity affect airflow into the lungs (3 marks).
The genioglossus is active during inspiration. When the activity of the genioglossus is decreased, inspiration will cause the tongue to flap over and cover the airway and therefore this decrease the airflow into the lungs.

2) Provide 4 pieces of evidence that supports the hypothesis that the pre-BotC is the respiratory nucleus responsible for causing breathing. Then provide 2 pieces of evidence that refutes this hypothesis. (12 marks)
(1) In the invtro slice that contains the pre-BotC, recording the hypoglossal nerve showed that a respiratory rhythm is generated and this rhythm is similar to that generated in an intact brainstem
(2) The pre-BotC can be visualized by injection of Ca^{2+} sensitive fluorescent dye. When cells are activated, Ca^{2+} flows into the cells and light them up. This experiment showed that the pre-BotC contained inspiratory neurons that discharge just before inspiration, which implies that they might induce inspiration.

(3) When the pre-BotC was isolated fromt he slice as a pre-BotC island, the cells continued to generate a respiratory rhythm
(4) When pre-BotC cells were inhibited by expressing AlstR and administration of allostatin, breathing stopped.

3) Generally describe and explain the 2 series of experiments that aimed to test the hypothesis that respiratory rhythm is generated by a network model. Based on these experiments explain which the 2 primary inhibitory neurotransmitters is most involved in controlling respiratory rhythm and provide evidence for this claim. (8 marks)
The network model predicts that the repiratory rhythm generation relies on synaptic inhibition between inspiratory and expiratory neurons. GABA and glycine cause synaptic inhibition by binding to their receptors which opens a Cl-channel that allows Cl to flow into the cell and cause hyperpolarization. The two experiments used GABA and glycine receptor antagonists bicuculline and strychinine, respectively, to block synaptic inhibition.

In an invitro experiment, application of bicuculline and strychinine disrupted the respiratory rhythm but didn't stop it.

In the invivo experiment, application of these antagonists stopped breathing. When strychinine was first applied it increased the respiratory frequency. Only when strychinine and bicuculline was applied together did the breathing stop. But when bicuculline was applied first (and alone), breathing stopped. Therefore GABA must be the most involved in controlling respiratory rhythm as its antagonists bicuculline was able to stop breathing on its own.

4) Explain how you would experimentally distinguish between inspiratory neurons that are pacemakers versus non-pacemakers. (6 marks)
First, depolarize both pacemakers and nonpacemakers with an electrical charge. Pacemakerc cells will increase its firing of action potential that correlates with respiration and also increase the amplitude. In nonpacemakers, they become more depolarized and fire action potentials randomly.

Second, add riluzole to both. Riluzole blocks the activity of pacemakers. When riluzole is added in increasing concentration, pacemakers' action potentials decrease in amplitude. Nonpacemakers are not affected.

5) Provide 2 pieces of evidence that support the hypothesis that the pre-Botzinger complex contains pacemaker neurons. Then provide 1 piece of evidence explaining whether or not pacemaker cells are responsible for generating inspiratory activity. (4 marks)

When the pre-BotC cells were isolated into a pre-BotC island the cells continue to generate a respiratory rhythm. This shows the cells have the biochemical requisites (pacemaker potentials) to keep firing and generating a respiratory rhythm.

Also when the pre-BotC was depolarized with electrical current, pacemakers increased their firing of action potentials that correlated with respiration. And antoehr group of cells that are nonpacemakers did not exhibit this. Instead, they just become more depolarized and fired action potentials at random. This shows that the pre-BotC contains both pacemaker and nonpacemaker cells.

Although the pre-BotC contains pacemaker cells, they are not critical for respiratory rhythm generation. When riluzole, which blocks pacemaker cells, was added to the pre-BotC, the respiratory frequency was unaltered.