Physiology 4560A
Integrative Neurophysiology
Fall term 2015

The brainstem and hypothalamus contribute to the neural integration of autonomic, endocrine and skeletomotor responses which in turn contribute to homeostatic and adaptive behaviours. This course will examine some of these regulatory and integrative responses in depth, with focus on whole animal, organ and cellular responses. Selected topics will focus on the central integration of cardiovascular function, ingestive behaviour and obesity, stress and sleep apnea.

**Course will consist of lectures followed by student presentations of selective research papers and paper discussions.**

**Lectures:** Wednesday/ 9:30-11:20 am/MSB 282

**Requisites:** Prerequisite(s): Physiology 3120 and Physiology 3140 or equivalent, or by special permission from Course Manager.

**Senate regulation regarding the student’s responsibility regarding requisites:**

Unless you have either the requisites for this course or written special permission from your Dean to enroll in it, you may be removed from this course and it will be deleted from your record. This decision may not be appealed. You will receive no adjustment to your fees in the event that you are dropped from a course for failing to have the necessary prerequisites.

*Please contact the course instructor if you require material in an alternate format or if any other arrangements can make this course more accessible to you. You may also wish to contact Services for Students with Disabilities (SSD) at 661-2111 x 82147 for any specific question regarding an accommodation.*

**Instructor Information**

Physiology 4650A is a team taught course by Dr. J. Ciriello and Dr. W. Inoue.
Dr. John Ciriello  
[john.ciriello@schulich.uwo.ca](mailto:john.ciriello@schulich.uwo.ca)  
Office: Medical Science Building M260  
Telephone: 519-661-3484

Dr. Waturu Inoue  
[winoue@uwo.ca](mailto:winoue@uwo.ca)  
Office: Robarts Research Institute 2741  
Telephone: 519.931.5777, Ext. 24373
Dr. John Ciriello is also the Course Manager for Physiology 4650A. His office is located on the second floor of the Medical Science Building (M 260) in the Schulich School of Medicine and Dentistry.

Feel free to drop by to discuss any aspect of the course (Monday 9:00 am to noon), but bear in mind that it is best to make an appointment beforehand. Your input is essential to making this an enjoyable learning experience.

OWL:  [https://owl.uwo.ca/portal](https://owl.uwo.ca/portal)
Once on the site, Log onto OWL using your UWO username and password. Select Human Physiology 4650A to get to the course website.

All announcements of importance, such as changes in exam room numbers or exam times and dates, exam results and all lecture notes will be posted on Web-CT under Announcements. Bookmark the website and access it on a regular basis to stay up-to-date as to periodic announcements.

OWL is NOT a forum in which professors will answer student questions concerning the lecture material. You must contact the Professor in question directly with any questions concerning the course or course material.

You may also want to download the additional Power Point Notes from the OWL site and bring them to the lectures for some of the lectures. Ideally, if you print the Power Point Notes in a 3 panels per page format, this will leave room for your hand-written notes on one side of the page in class.

If you have any questions or experience any OWL issues, please email owl@uwo.ca.

Course Syllabus
General Objectives of the Course:

a. To attain a general understanding of contemporary regulatory and integrative neurophysiology.

b. To appreciate the importance of the approach of regulatory physiology in formulating an appropriate conceptual framework of value in organizing existing knowledge and in research.

c. To consider in some depth examples of physiological regulations (e.g. hypertension, obesity, stress and sleep apnea), and to assess research publications in these fields by student-driven presentations and discussions.

d. To increase your knowledge of neural and endocrine mechanisms associated with physiological regulations and behavioural adaptations. You will gain a good understanding of the functional anatomy and physiology of the autonomic
nervous system, the brainstem and hypothalamus, forebrain limbic structures, aspects of neuroendocrinology relevant to the examples of physiological regulations considered in the course, and sex differences in brainstem and hypothalamic control mechanisms.

Lecture: 1. September 16/15 - Dr. J. Ciriello - 9:30 - 10:20 am

INTRODUCTION AND COURSE EXPECTATIONS.

Lecture: 2. September 16/15 - Drs. J. Ciriello - 10:30 - 11:20 am

THE AUTONOMIC NERVOUS SYSTEM AND BARORECEPTOR REFLEX: OVERVIEW.

Body functions, which normally proceed independently of volitional activity, are regulated in part by reflex mechanisms that are served by afferent, efferent, and central integrating structures. Collectively, these structures form what Reil first described in 1857 as the "vegetative" or "autonomic" nervous system. Neurons of the autonomic nervous system innervate cardiac muscle, smooth muscle and glands. Anatomical and physiological differences within the autonomic nervous system are the basis for its further subdivision into sympathetic and parasympathetic components. The heart, blood vessels and glands are mostly innervated by both components and because these organs and tissues participate as effectors in almost all bodily functions, it follows that the autonomic nervous system has an extremely important role in the homeostatic control of the internal environment. Although this system is essentially autonomous, it is not entirely free from voluntary control, as autonomic reflexes and glandular secretions can be learned and modified and are thus also under cerebral cortical control.

In today's lecture, we will begin by reviewing the anatomical components of the autonomic nervous system. We will also examine some of the functional properties of these components. Finally, some of the anatomical and physiological properties of the sympathetic and parasympathetic pre-ganglionic neuron, the final common pathway from central structures controlling autonomic function will be reviewed.

We will also review both the anatomical and functional properties of the baroreceptor and chemoreceptor reflexes by examining the afferent neuronal system that relays information regarding cardiovascular variables (arterial pressure and blood O₂ and CO₂ tension) to the central nervous system.

The following readings may be useful in helping to clarify some points for lectures III-VI.


Lecture: 3. September 23/15 - Dr. J. Ciriello - 9:30 - 10:20 am

THE NUCLEUS OF THE SOLITARY TRACT AND THE VENTROLATERAL MEDULLA.

We will review the contribution of the nucleus of the solitary tract, the primary site of termination of cardiovascular afferent fibers in the central nervous system involved in the baroreceptor reflex on circulatory function and the effect of some putative transmitters involved in modulating the baroreceptor reflex. We will also examine the central neuronal circuitry that is involved in this reflex arc, how this reflex arc is affected by circulating sex steroids and how changes in the transmission of baroreceptor afferent information in the brain can contribute to the development of hypertension.

In addition, one aspect of central control of the circulation that has emerged is the elucidation of neuronal circuits that are specifically responsible for the generation of sympathetic tone, and how changes in these central neuronal processes contribute to the disease of hypertension. Neuronal circuits controlling the circulation are found throughout the neuroaxis, but it now appears that the most important are located in the ventral lateral aspects of the medulla oblongata. This area is thought to be the classical vasomotor centre of the brain. In this lecture we will review some of the functional properties of ventrolateral medullary neurons, their connectivity and their neurochemistry. Finally, we will examine how command signals originating in this medullary structure contribute to a chronic elevation in arterial pressure.


SEX DIFFERENCES IN BRAINSTEM and FOREBRAIN CONTROL MECHANISMS

It has been apparent for a number of years that little attention has been given to sex differences in the control of autonomic function. This lecture will focus on how cardiovascular control systems discussed in the previous hour vary between the sexes.


SEX DIFFERENCES IN CONTROL MECHANISMS – Cont’d.
In these two lectures we will continue with the theme of sex differences in central control mechanisms by examining anatomical and functional differences that exist within the forebrain. The lectures will focus on sex differences in autonomic, neuroendocrine and stress related mechanisms controlled by the hypothalamus and limbic system.


Student presentations related to sex differences in brainstem and forebrain mechanism. Presentations: TBA


THE HYPOTHALAMUS: CIRCULATORY REGULATION AND HYPERTENSION.

During this session we will examine the contribution of hypothalamic and other forebrain structures in the control of the circulation. Although virtually the whole brain is involved in maintaining the internal environment constant, neurons involved in homeostasis are concentrated within the hypothalamus. Because of this, the hypothalamus has often been called the "head ganglion" of the autonomic nervous system.

The limbic structures, in association with the hypothalamus, contributes to higher order integration of autonomic, endocrine and behavioural responses for homeostatic regulation of the internal environment for the adaptation of the animal to the continuously changing external environment. The neural integrative activities of these structures ensure that the "house-keeping chores" occur routinely in relation to the varying demands of the behaving animal.

We will examine some of the evidence that indicates that a malfunction in the neuronal circuits within the hypothalamus and limbic system that control the circulation is involved in the hypertensive process. We will examine the connectivity of the hypothalamus, the physiological functions generally controlled by the hypothalamus and the direct role of some hypothalamic nuclei in controlling sympathetic nervous system activity.

These are readings that may be useful in helping to clarify some points. They contain much of the information we will discuss in lectures.


Lectures: 11. October 21/15 – Dr. J. Ciriello - 9:30 - 10:20

THE BRAIN RENIN-ANGIOTENSIN SYSTEM AND CIRCUMVENTRICULAR ORGANS.

In addition to those components of the renin-angiotensin system found within the peripheral circulation, all components of the renin-angiotensin system have been identified in the brain. Central angiotensin exerts its effects predominantly within the hypothalamus on neuronal groups controlling body fluid balance, blood volume and blood pressure. Angiotensin within the systemic circulation can also exert effects on the hypothalamus by activating specialized brain structures called circumventricular organs (CVO’s). Normally, the capillaries of the brain form a unique barrier that permits only specific molecules or ions to be transported across the endothelial cells, thus creating a blood-brain barrier. This barrier is present throughout the brain except in a few specialized midline structures along the third and fourth ventricle of the brain. These structures, the CVO’s, lack a functional blood-brain barrier. They allow a variety of small molecules to pass through fenestrated capillaries to gain direct access to the nervous tissue. These central CVO structures include the subfornical organ, the organum vasculosum of the laminae terminalis, area postrema, median eminence and pineal gland. The first three structures have neurons that project to and make synaptic connections with other areas in the central nervous system. Thus these CVO’s can exert profound effects on the neuronal circuits controlling endocrine and autonomic function, and behaviour. We will examine some of the evidence indicating the role of these CVO’s in fluid balance and blood pressure regulation. In addition, we will examine some of the evidence indicating that activation of these systems may lead to the development of hypertension but altering the activity of other brainstem or forebrain structures.

The following reading may be useful in helping to clarify some points.


Lecture 12: October 21/15 - Dr. J. Ciriello - 9:30 - 10:20

THE HYPOTHALAMUS: CIRCULATORY REGULATION AND HYPERTENSION. Student Presentations: TBA

BODY ENERGY BALANCE.

The regulation of “Total Body Energy” is not well understood. A 1% error in the balance between intake of body energy and energy expenditure would result in an approximate doubling of our body weight each year. We now face an obesity “epidemic” in the Western world. In recent years, no other hormone has drawn more attention than LEPTIN on the control of appetite, body weight and obesity. This hormone, produced by adipose tissue, enters the brain via a saturable specific transport mechanism. Leptin acts at the hypothalamus to modulate food intake, heat production, hormonal release and the autonomic nervous system. In addition to leptin, the newly discovered peptide OREXIN, has been shown to be involved in ingestive behaviours. This peptide is selectively found only within hypothalamic neurons.

In this session we will examine the overall control of energy balance together with elements which are involved in this regulation, including physical, biochemical, physiological and behavioural mechanisms.

These are readings that may be useful in helping to clarify some points.


BODY ENERGY BALANCE. Student Presentations-TBA


CENTRAL MECHANISMS IN OBESITY RELATED HYPERTENSION.

The mechanisms by which overweight is translated into insulin resistance, hypertension and diabetes are currently being investigated. Although the interactions among factors contributing to these disease processes are not entirely clear, it is known that a major consequence of obesity is an increased activation of the sympathetic nervous system. This is consistent with reports showing that a caloric restriction leads to a decrease in arterial pressure. In this lecture we will examine the contribution of these compounds on central mechanisms that control arterial pressure.
These are readings that may be useful in helping to clarify some points.


CENTRAL MECHANISMS IN OBESITY RELATED HYPERTENSION. Student Presentations: TBA

Lectures: 19. November 18/15. - Dr. Wataru Inoue- 9:30 - 10:20

STRESS RESPONSE: AN OVERVIEW

In biology, stress is defined as “an organism’s total response to stimuli that threaten its well-being”. Here, ‘total’ response means a collection of both psychological (e.g. alertness, aggression) and physiological (e.g. increases of heart rate, blood pressure and metabolism) changes that are recruited in order to cope with an impending challenge (stressor). Accordingly, various areas of the brain are involved in driving stress response, and the brain in turn interacts with various parts of the body. Within this highly integrated biological mechanism, key elements are the activations of the sympathetic nervous system (i.e. fight-or-flight response) and the hypothalamic-pituitary-adrenal (HPA) axis (i.e. neuroendocrine stress response). In this lecture, we will discuss an overview of these two systems, from their anatomical basis, regulatory mechanisms, and the roles of their effector molecules (nor)adrenaline and glucocorticoids in mediating stress response. In addition to driving the immediate reactions to a challenge, stress, in particular chronic stress, imposes protracted effects on the body and could contribute to various pathologies. In this context, we will discuss the neuroendocrine stress response and the heterogeneous (good and bad) actions of glucocorticoids that lead to both adaptive and maladaptive consequences.

References:

Lecture 20: November 18/15. - Dr. Wataru Inoue- 10:30 - 10:20

THE PARAVENTRICULAR NUCLEUS OF THE HYPOTHALAMUS: THE CONTROLLER OF PHYSIOLOGICAL RESPONSE TO STRESS

Stressors can take various forms, for example psychological (i.e. exam) or physiological (i.e. injury). These different modalities of sensory information are processed in different brain areas, yet eventually drive the common physiological responses; the activation of the sympathetic nervous system and the HPA axis. The paraventricular nucleus of the hypothalamus (PVN) regulates both of the common stress responses following a wide range of stressor, thereby serving as a key integrator of stress information. In this lecture, we will review the anatomical components and functional properties of neural circuits that feed into the PVN for this stress information integration. This is an area of active research, and there are still much more to be clarified. We will start our discussion from some of the classic researches and then move onto the latest advances using a new technology optogenetics.

References:

Lecture 21-22: November 25/15. - Dr. Wataru Inoue- 9:30 - 11:20

NEUROBIOLOGY OF STRESS- Student presentations: TBA

Lecture 23: December 02/15. - Dr. Wataru Inoue- 9:30 - 10:20

NEUROBIOLOGY OF STRESS ADAPTATION

Stress response is versatile and dynamic, and prior stressful experiences constantly reshape subsequent stress responses. In other words, organisms learn and remember stress. At mechanistic levels, this ‘learning’ involves neurochemical, synaptic
and structural changes in neural circuits underlying the stress response. Indeed, the actions of the mediators of stress (e.g. glucocorticoids) strongly modulate the cellular and molecular mechanisms of neuroplasticity such as neurogenesis, structural remodeling and synaptic plasticity. We will discuss how the actions of stress mediators mediate/modulate neuroplasticity, and as a consequence change future stress responses. We will also discuss the implications of these mechanisms in the detrimental consequences of stress, such as memory impairment and the development of mood disorders.

Reference:

Lecture 24: December 02/15. - Dr. Wataru Inoue- 10:30 - 11:20

NEUROBIOLOGY OF STRESS- Student presentations: TBA


SLEEP APNEA AND AUTONOMIC CONSEQUENCES.

Obstructive Sleep Apnea (OSA) is the most common form of breathing sleep disorder. OSA is characterized by the repetitive cessation of respiratory airflow resulting from upper pharyngeal airway collapse and obstruction. The resulting apnea primarily induces intermittent hypoxia and hypercapnia, and the decreased haemoglobin oxygen saturation results in myocardial and systemic hypoxemia. OSA has been shown to occur in a considerable percentage of the population. It is estimated that 24% and 9% of middle age men and women, respectively, suffer from OSA, although the number of women that suffer from OSA increases considerably after menopause. There are now considerable data indicating that a significant number of adolescents also suffer from OSA. Untreated, the initial consequences of OSA are sleepiness and an associated decrease in the quality of life as a result of the sleep fragmentation. However, there are now clinical data suggesting that OSA may have direct and long term deleterious effects on cardiovascular function and structure through several mechanisms, including sympathetic activation due to activation of chemoreceptors, oxidative stress, inflammation, and endothelial dysfunction. OSA has been shown to be associated with atherosclerosis and coronary heart disease, cardiac arrhythmias, diabetes mellitus, and stroke and transient ischemic attacks. In this series of lectures we will examine the effects of OSA on neuronal circuits involved in regulating blood pressure and body weight.

These are readings that may be useful in helping to clarify some points.


RELATIONSHIP BETWEEN OBESITY, HYPERTENSION AND SLEEP APNEA. Student Presentations: TBA


Note that December 09/14 is the LAST DAY of class for this semester.

Course Materials

Textbook: No textbook required for the course. Selected papers for review can be obtained through library services.

You may also want to download the Power Point Notes from the course web site and bring them to the lectures. Ideally, if you print the Power Point Notes in a 3 panels per page format, this will leave room for your hand-written notes on one side of the page in class. Power Point Notes for a lecture will be placed on web-ct normally a week ahead of the scheduled class.

Evaluation:

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<th>Component</th>
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<td>25</td>
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<td>Research Paper Presentation</td>
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<td>Short Lay Summaries</td>
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Additional Information/Statements
Statement on Academic Offences
“Scholastic offences are taken seriously and students are directed to read the appropriate policy, specifically, the definition of what constitutes a Scholastic Offence, at the following website:
http://www.uwo.ca/univsec/handbook/appeals/scholastic_discipline_undergrad.pdf

With regards to major course assignment, please NOTE:
“All required papers may be subject to submission for textual similarity review to the commercial plagiarism detection software under license to the University for the detection of plagiarism. All papers submitted for such checking will be included as source documents in the reference database for the purpose of detecting plagiarism of papers subsequently submitted to the system. Use of the service is subject to the licensing agreement, currently between The University of Western Ontario and Turnitin.com (http://www.turnitin.com).”

Absence from course commitments

A. Absence for medical illness:

Information about “Accommodation for Medical Illness – Undergraduates: POLICY ON ACCOMMODATION FOR MEDICAL ILLNESS - UNDERGRADUATE STUDENTS” can be found in the Academic Handbook at
http://www.uwo.ca/univsec/handbook/appeals/accommodation_medical.pdf

Students must familiarize themselves with the Policy on Accommodation for Medical Illness:
https://studentservices.uwo.ca/secure/index.cfm

Statement from the Dean’s Office, Faculty of Science
If you are unable to meet a course requirement due to illness or other serious circumstances, you must provide valid medical or other supporting documentation to the Dean's office as soon as possible and contact your instructor immediately. It is the student's responsibility to make alternative arrangements with their instructor once the accommodation has been approved and the instructor has been informed. In the event of a missed final exam, a "Recommendation of Special Examination" form must be obtained from the Dean's Office immediately. For further information please see:

A student requiring academic accommodation due to illness, should use the Student Medical Certificate when visiting an off-campus medical facility or request a Record's Release Form (located in the Dean's Office) for visits to Student Health Services.
The form can be found at: https://studentservices.uwo.ca/secure/medical_document.pdf

The Policy on Accommodation for Medical Illness is also available on the BMSUE secure site: http://www.uwo.ca/bmsc/

Documentation is required for all missed tests, research paper presentations or assignments regardless of the mark value. Such documentation must be submitted by the student directly to the appropriate Faculty Dean`s Office and NOT to the instructor. It will subsequently be the Dean`s Office that will determine if accommodation is warranted.

For missed tests and presentations, the major assignment paper will be re-weighted accordingly when appropriate documentation is provided for the missing tests or presentations. With regards to the major assignment, a late submission will result in the final grade achieved reduced by one grade level lower.

B. Absence for non-medical reasons:

For non-medical absences from tests, research paper presentations, late assignments, documentation is still required, and such documentation must be submitted by the student directly to the appropriate Faculty Dean`s Office and NOT to the instructor. It will subsequently be the Dean`s Office that will determine if accommodation is warranted.

C. Special Examinations

A Special Examination is any examination other than the regular examination, and it may be offered only with the permission of the Dean of the Faculty in which the student is registered, in consultation with the instructor and Department Chair. Permission to write a Special Examination may be given on the basis of compassionate or medical grounds with appropriate supporting documents.

A Special Examination must be written at the University or an Affiliated University College no later than 30 days after the end of the examination period involved. To accommodate unusual circumstances, a date later than this may be arranged at the time permission is first given by the Dean of the Faculty. The Dean will consult with the instructor and Department Chair and, if a later date is arranged, will communicate this to Registrarial Services.

If a student fails to write a scheduled Special Examination, permission to write another Special Examination will be granted only with the permission of the Dean in exceptional circumstances and with appropriate supporting documents. In such a case, the date of this Special Examination normally will be the scheduled date for the final exam the next time the course is offered.

Support Services:
Registrarial Services: http://www.registrar.uwo.ca

Academic Counselling (Science and Basic Medical Sciences): http://www.uwo.ca/sci/counselling/

USC Student Support Services: http://westernusc.ca/services/

Student Development Services: http://www.sds.uwo.ca

Student Health Services: http://www.shs.uwo.ca/

Students that are in emotion/mental distress should refer to Mental Health@Western http://www.uwo.ca/uwocom/mentalhealth/ for a complete list of option about how to obtain help.