Teaching the interrelationship between stress, emotions, and cardiovascular risk using a classic paper by Walter Cannon

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Gwirtz PA. Teaching the interrelationship between stress, emotions, and cardiovascular risk using a classic paper by Walter Cannon. *Adv Physiol Educ* 32: 18–22, 2008; doi:10.1152/advan.00051.2007.—Classroom discussion of the classic article by Walter B. Cannon in 1914, entitled “The emergency function of the adrenal medulla in pain and the major emotions,” is an excellent tool to teach graduate students the interaction between stress, emotions, and cardiovascular function. Using this article, we are able to review important early research by Dr. Cannon, including discussion of his scientific methods and results and how they hold true today. This article outlines how this classic paper is used to allow students to explore basics principles of cardiovascular control during stress. The teaching points that are presented illustrate how students can be directed to understand the interrelationship between chronic stress and cardiovascular disease.

epinephrine; adrenal

THE CARDIOVASCULAR RESPONSE to stressful states is of great interest to students of physiology and psychology. It has been known for over a century that the release of epinephrine from the adrenal medulla in response to sympathetic stimulation produces many of the cardiovascular effects occurring during such conditions as fear, pain, and rage (2). A series of experiments by Walter B. Cannon and his students culminating in this classic paper addressed an important question regarding the physiological purpose of this sympathetic reflex (6). This paper, which is part of the American Physiological Society Legacy Project (http://www.the-aps.org/publications/legacy/), has been useful in teaching the principles of sympathetic reflex control of the cardiovascular system during stressful situations to graduate students. This graduate-level course first focuses on reviewing the current understanding of the normal physiology of the cardiovascular system. We then examine the cardiovascular response to stress and the role of stress as an important cardiovascular risk factor for cardiovascular disease (CVD).

Cardiovascular Control Systems and Homeostasis

The control of cardiovascular function has received much attention for over 100 years. CVD is the leading cause of death, disability, and suffering of men and women in the United States and other industrialized countries (1, 10). There has been a global rise in CVD over the last century due to changing socioeconomic circumstances, decreased pandemics, urbanization, and changes in work-related activities, all of which have resulted in lifestyle changes in diet, activity levels, and behaviors such as smoking. The role of various cardiovascular risk factors in causing CVD is well known and has led physicians and scientists to develop and implement new methodologies and techniques to treat and/or actually prevent CVD. This has been a multidisciplinary effort involving both biomedical, behavioral, and social sciences, and many of these efforts have been successful. Thus, mortality due to CVD had decreased by 25% over the last 10 years (1, 10).

CVD usually represents a disease process due to slow accumulation of damage. The study of CVD in this course allows the student to recognize the complex interrelationship between our biology and emotions and how extreme emotional disturbances can adversely affect us. Centuries ago, physicians recognized the role of individual differences in vulnerability to and recovery from disease. Claude Bernard recognized in 1865 that the internal environment (“le milieu intérieur”) is much more stable in its properties than the always-changing external environment that envelops the whole organism (3, 4). He maintained that this stability is necessary for a free and independent life. Early in the 20th century, Dr. Walter Cannon expanded this concept with regard to the role of physiological regulation in achieving the constancy that Bernard first described (6–9). Cannon is well known for his study of mechanisms involved in regulating the internal environment of the body and for coining the term “homeostasis.” Homeostasis is a concept that states that all sorts of physiological variables are being kept at an optimal level or within narrow ranges by the actions of homeostatic control mechanisms. Cannon also scientifically examined how the body responds to stressful events and its relationship to CVD. Although Cannon never used the term “fight or flight,” his article explores the role of the adrenal medulla in controlling visceral function during emotional excitement (6). There is now much physiological, biochemical, and molecular information available regarding how emotional stress, turmoil, psychological characteristics, socioeconomic status, and the sort of society in which we live can affect body functions, such as the development of atherosclerosis and hypertension. These are all explored by the student in this course.

Dramatic advances have been made demonstrating that aggressive medical therapy will substantially reduce the likelihood of recurrent major coronary syndromes in patients with established coronary heart disease (secondary prevention) (11). The major and independent risk factors for CVD include cigarette smoking, elevated blood pressure, elevated serum total and LDL-cholesterol, low serum HDL-cholesterol, diabetes mellitus, and advancing age (11). Conditional or predisposing risk factors are those that worsen the independent risk factors and include obesity, abdominal obesity, physical inactivity, family history of premature coronary heart disease, and ethnic characteristics. Risk factors for CVD also include so-
How would you design these experiments today; what would you do differently and would you obtain similar results?

Compare and contrast the writing style used by Cannon in 1914 vs. the style used by authors who publish in the present day.

Would the experimental design and methods used to evoke the major emotions of fear, pain, and asphyxia be approved by an Institutional Animal Care and Use Committee today?

Discuss issues of animal use in research and the methods used in this paper. Describe the methods of the study of emotions by Cannon.

What are the roles of epinephrine and blood sugar in the response to exertion? How does this compare with the cardiovascular, respiratory, and digestive responses occurring during pain, rage, and fear described by more recent or modern studies?

What is the purpose of these reflexes in maintaining homeostasis?

What cardiac and vascular changes are produced by epinephrine during muscle exertion?

What are the roles of epinephrine and blood sugar in the response to exertion? How does this compare with the cardiovascular, respiratory, and digestive responses occurring during pain, rage, and fear described by more recent or modern studies?

What is the physiological importance of the results of these studies? Is behavior (i.e., how we respond to major emotional stimuli) a major modifiable risk factor for CVD leading to progression and/or regression of atherosclerosis and how?

How can patients with CVD benefit from modifying their response to stress with regard to improved quality of life?

CVD, cardiovascular disease.

cocioeconomic and psychosocial factors. Thus, treatment must also involve psychosocial management, which involves identifying problems such as depression, anxiety, social isolation, anger, hostility, and stress, and incorporating counseling patients regarding psychosocial problems, stress management skills, and coping skills.

There is a strong interrelationship between biology and emotions (2). There are many ways in which personality and thoughts (the psyche) both reflect and influence physiology. Intense emotions such as anger or hostility, anxiety, and elation affect the heart and circulatory system directly through the autonomic nervous system and indirectly by neuroendocrine pathways. Studies have strongly indicated that emotional and psychosocial factors strongly influence the development of disease and the outcome of therapy in patients with CVD. Sir William Osler noted the importance of psychological stress when he wrote the following in 1897 (5):

"...In the worry and strain of modern life arterial degeneration is not only very common, but develops often at a relatively early age. For this I believe that the high pressure at which men live, and the habit of working the machine to its maximum capacity, are responsible, rather than excesses in eating or drinking."

Thus, psychological risk factors for CVD have been known for a long time. Since the 1800’s, much physiological, biochemical, and molecular information has become available regarding how many intangibles in our lives (emotional, turmoil), psychological characteristics, psychosocial status, and the society in which we live can adversely affect body functions. For example, depression, hostility, and perceived lack of social support are common in patients with CVD and, as a result, are associated with increased cardiac morbidity and mortality by eightfold (2). Depression is also a very common occurrence after myocardial infarction and thus increases the risk of a future cardiac event. Pioneering work by Cannon examined how the body responds to stressful events and its relationship to CVD; this article emphasizes the mechanism by which the body adapts to a stress response.

Teaching Points

This classic paper by Dr. Cannon is useful in teaching students the principles of the interrelationship between emotions, homeostasis, and cardiovascular function, as mentioned above. Dr. Cannon emphasized the adaptations of the body to various stresses, such pain, fear, rage, and asphyxia. His classic studies challenged popular ideas of his time and paved the way for future work by Selye and Fortier (13–19), Sterling and Eyer (20), McEwen and Stellar (12), and others and demonstrated the changes that occur in response to a stress, i.e., the “flight-or-flight response.” It is important for students to not just acquire information from the articles and books that they read.

Table 1. Teaching points

<table>
<thead>
<tr>
<th>Questions Related to the Classic Paper of Dr. Cannon (8)</th>
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<tr>
<td>- Define physiological stress and psychological stress and describe the cardiovascular responses to these stresses.</td>
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<td>- Cannon described responses to four emotional stresses. Describe the experimental models used by Cannon to induce stress and to determine how epinephrine is released by the adrenal medulla and the effects of epinephrine on the body.</td>
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<td>- What were the responses Cannon observed when he induced pain, fear, rage, and asphyxia? How were the results altered if the adrenal medulla was removed?</td>
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<td>- Relate the responses found by Cannon to the current understanding of the response to stress.</td>
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<td>- How might the responses to physiological and psychological stresses be different in patients with existing CVD, e.g., atherosclerosis, hypertension, and heart failure, or in patients with one or more cardiovascular risk factors?</td>
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<td>- Discuss the impact of depression, socioeconomic status, gender, and existence of other cardiovascular risk factors on the response to emotional stress.</td>
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<td>- Discuss what Cannon described as the natural events in life that result in epinephrine release and how these are related to cardiovascular risk.</td>
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<td>- Explain Cannon’s concept that “these bodily reactions to pain and to emotion-provoking objects is that they are of the nature of reflexes,–they are not willed movements, indeed they are often distressingly beyond the control of will.”</td>
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<td>- What cardiac and vascular changes are produced by epinephrine during muscle exertion?</td>
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Table 2. Questions for discovery learning

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<tr>
<td>- Draw your own graphs based on Cannon’s data, including sympathetic nervous system outflow, mean arterial blood pressure, heart rate, plasma levels of epinephrine and glucose, glycogen stores in the skeletal muscle and liver, and vascular resistance in the heart, lungs, brain, splanchnic region, skeletal muscle, and kidney.</td>
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<tr>
<td>- Discuss issues of animal use in research and the methods used in this paper. Describe the methods of the study of emotions by Cannon.</td>
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<td>- Would the experimental design and methods used to evoke the major emotions of fear, pain, and asphyxia be approved by an Institutional Animal Care and Use Committee today?</td>
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<tr>
<td>- Compare and contrast the writing style used by Cannon in 1914 vs. the style used by authors who publish in the American Journal of Physiology today.</td>
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<td>- Discuss the differences in how investigators would design this study today, based on the Institutional Animal Care and Use Committee, Association for the Accreditation of Laboratory Animal Care, United States Department of Agriculture, Internal Review Board, and Federal Drug Administration.</td>
</tr>
<tr>
<td>- How would you design these experiments today; what would you do differently and would you obtain similar results?</td>
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Using Classic Papers to Teach Physiology
but to also actively apply concepts and principles by participation through questions and answers and by getting timely feedback about their performance. With these learning strategies in mind, several teaching points can be used when discussing Dr. Cannon’s paper with students. As the students read the paper, they are asked to answer a series of questions that focus on Cannon’s main ideas. The discussion topics are summarized in Tables 1 and 2 and are discussed below.

Teaching point 1. First, students are asked to define physiological stress and psychological stress. This requires the students to explain the changes that occur in the body in response to these stresses, including neural, cardiac, vascular, hormonal, respiratory, and digestive responses.

Teaching point 2. Discuss the changes described by Cannon in response to the release of epinephrine when the following emotional states are provoked: pain, fear, rage, and asphyxia. Students are then able to evaluate the contribution by Cannon and his colleagues in the early 1900s to the current understanding of the response to stress.

Teaching point 3. Students are then asked to take this analysis further by discussing how the response might be different in patients with existing CVD, e.g., atherosclerosis, hypertension, and heart failure or in patients with one or more cardiovascular risk factors.

Teaching point 4. Taking the analysis further, we then discuss the impact of depression, socioeconomic status, gender, and existence of other cardiovascular risk factors on the cardiovascular response to emotional stress. We consider not only the role of stress as a causative factor in CVD but also how CVD may impose significant stress in a patient and affect outcome.

Teaching point 5. It is important for students to appreciate the design of experimental models based on available technology and how experimental design has changed during the last century. Students are asked to describe the experimental models that were used by Cannon to induce stress, determine how epinephrine is released by the adrenal medulla, and the effect of the epinephrine on the body. What were Cannon’s observations and how did he conduct these studies, including blood sugar, during fear, rage, asphyxia, and pain? How were the results altered if the adrenal medulla was removed? How would the student design these experiments today; what would they do differently and would they obtain similar results? Usually, the students arrive at the conclusion that despite limitations to Cannon’s experimental approach, his conclusions are valid today.

Teaching point 6. We then discuss what Cannon described as the natural events in life that result in epinephrine release and how these are related to cardiovascular risk. A discussion follows regarding Cannon’s view that “...the absolutely essential organs—the ‘tripod of life’—the heart, lungs and brain (as well as the skeletal muscles)—are, in times of excitement, when the adrenal glands discharge, abundantly supplied with blood taken from organs of less importance in critical moments.” Despite his views being challenged by other investigators, this concept first voiced by Cannon appears in physiology textbooks today as an important homeostatic mechanism operating during physiological and emotional stresses.

Teaching point 7. Students are asked to describe the neurohumoral reflex nature of bodily response to pain and major emotions as described in this paper. Cannon asked the question “whether the medulla is stimulated to activity by nervous impulses aroused by the natural events in the course of an animal’s life” and found that the adrenal medulla released epinephrine in response to fear, pain stimulation of the sciatic nerve, and asphyxia. He also reported that “these bodily reactions to pain and to emotion-provoking objects is that they are
of the nature of reflexes—they are not willed movements, indeed they are often distressingly beyond the control of the will.” Students are asked to explain this concept and the purpose of these reflexes in maintaining homeostasis. In that regard, what cardiac and vascular changes are produced by epinephrine during muscular exertion? What is the role of epinephrine and blood sugar in these responses? How does this compare with the cardiovascular, respiratory, and digestive responses occurring during pain, rage, and fear described by more recent or “modern” studies?

Teaching point 8. Finally, we address the physiological importance of the results of these studies. Is behavior (i.e., how we respond to major emotional stimuli) a major modifiable risk factor for CVD leading to prevention and/or regression of atherosclerosis and how? How can patients with CVD benefit from modifying their response to stress with regard to improved quality of life?

Questions for Learning Discovery

Questions for learning discovery are shown in Table 2. Since Cannon’s article contains no graphs or figures, the students are asked to draw their own graphs and figures depicting Cannon’s data and discuss their approach to statistical analysis of the results. Typical graphs before and after removal of the adrenal gland presented by students are shown in Fig. 1. These graphs are to include the following responses to pain, fear, rage, and asphyxia: sympathetic nervous system outflow, blood pressure, heart rate, plasma epinephrine levels, blood glucose levels, skeletal muscle and liver stores of glycogen, and blood flow to the heart, lungs, brain, splanchnic organs, skeletal muscle. Taking this a step further, I ask them to graph the responses to physical exertion as well. The students were positively challenged by this aspect of the exercise since it requires an active application of the concepts and principles and developing them into a picture. I believe that this activity is important in that it requires the students to demonstrate that they have acquired appropriate concepts as applicable to visceral reflexes.

In addition to addressing questions related directly to the aims, methods, and results of the paper, the classroom discussion also addresses additional topics. For example, I ask students to compare and contrast the writing style used by Cannon in 1914 vs. the style used by authors who publish in the American Journal of Physiology today. For example, this paper is not divided into introduction, methods, results, or discussion sections, and there are no tables or figures presenting the data. In contrast to studies published today, there are no stated hypotheses.

We also address the issues of animal use in research. This offers an opportunity to review animal care and use protocol review by Institutional Animal Care and Use Committees (IACUCs) to be in compliance with Association for the Accreditation of Laboratory Animal Care (AAALAC) and United States Department of Agriculture (USDA) guidelines and protection of human subjects in research and the role of the Internal Review Board (IRB) and Federal Drug Administration (FDA). Students are asked to discuss the methods of study of emotions by Cannon. Would the experimental design and methods used to evoke the major emotions of fear and pain and asphyxia be approved by an IACUC today? This finally leads to a discussion regarding differences in how investigators would design this study today, based on IACUC, AAALAC, USDA, IRB, and FDA and regulations.

Student Feedback

Students received this series of sessions enthusiastically. Students will always rise to a challenge, and my students always came prepared to class and enjoyed a lively discussion. Comments written back to me regarding this method of teaching is that it is challenging, forces them to think outside of the box, and forces them to apply the general concepts that they learn in this course as well as in others. Students also comment regarding how this teaching approach does enhance their learning and understanding of the material. This was demonstrated a year later when taking their oral and written progress/qualifying exams. Students exclaimed that many of their questions related to the material covered by this course and that the teaching approach taken in this section of the course enhanced their ability to retain their knowledge and apply it to answering the exam questions. I also received comments in the course critique that indicated that studying this classic paper increased their appreciation of historical research and its contribution to physiology and did contribute to their understanding of contemporary physiology.

In summary, Cannon pioneered the studies of how an organism responds to disturbances that may disrupt homeostasis. Recognition of his important contribution and careful examination of his research will provide students with an understanding of the complex neurohumoral reflex nature of homeostatic control. Use of this paper will allow students to gain an appreciation of experimental design and physiological integration and application.

REFERENCES