American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 14, No 11 (November), 2013: pp 1349-1360
Available online at www.jpain.org and www.sciencedirect.com

Beta-Adrenergic Receptor Mechanisms and Pain Sensitivity in Women With Menstrually Related Mood Disorders

Adomas Bunevicius,* Alan Hinderliter,† Rebecca Klatzkin,‡ Ankit Patel,† Cara Arizmendi,* and Susan S. Girdler*

**Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.*
†Department of Medicine, Division of Cardiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
‡Department of Psychology at Rhodes College, Memphis, Tennessee.

Abstract: **Somatic symptoms experienced by women with a menstrually related mood disorder (MRMD) during their premenstrual luteal phase contribute to functional impairment. Yet, investigations on pathophysiological mechanisms contributing to heightened pain sensitivity in MRMD are sparse. During the luteal phase, 61 women with an MRMD and 61 non-MRMD controls were evaluated for β-adrenergic receptor (β-AR) responsivity using the isoproterenol sensitivity test. A subset (43 MRMD and 50 non-MRMD) then entered a double-blind, placebo-controlled, crossover protocol to examine the effect of β-AR blockade with intravenous propranolol on sensitivity to experimental (cold pressor and ischemic) and clinical (McGill Pain Questionnaire score) pain. Women with an MRMD exhibited greater β_1- and β_2-AR responsivity, ischemic pain intensity, and affective clinical pain ratings than controls. Propranolol increased cold pressor pain tolerance in both groups, but it decreased cold pain intensity and ischemic pain unpleasantness ratings only in non-MRMD women. In contrast, propranolol decreased affective ratings of clinical pain in women with MRMD. Exploratory analyses indicated that only in MRMD women did greater β-AR responsivity predict greater sensitivity to cold pressor and ischemic pain. This study provides the first evidence for a role of β-AR mechanisms in the hyperalgesia and clinical pain experienced by women with MRMDs.**

***Perspective:** This article describes the effects of β-adrenergic receptor stimulation and blockade on experimental and clinical pain sensitivity in women with an MRMD. The results of this study may have implications for the management of the substantial somatic premenstrual symptomatology experienced by women with an MRMD.*

Key words: *β-adrenergic receptors, pain sensitivity, propranolol, menstrually related mood disorders.*

Menstrually related mood disorders (MRMDs) represent a constellation of psychological and physical symptoms that are isolated to the premenstrual (luteal) phase of the menstrual cycle, are accompanied by substantial functional impairment, and remit with the onset of menstruation.[11,13] Up to 30% of women in their reproductive years experience an MRMD, and up to 8% of women experience premenstrual dysphoric disorder (PMDD), the most severe form of MRMDs.[3,34,60] The disability-adjusted life years lost due to a repeated-cyclic MRMD is of the same magnitude as major recognized disorders[34] and is associated with risk of suicide attempts.[76]

Pathophysiological factors implicated in MRMDs include dysregulation in β-adrenergic receptor (AR) mechanisms. β-ARs are known for their role in cardiovascular, airway, uterine, and metabolic functions; however, they are also densely distributed in the central nervous system and play an important role in sympathetic tone regulation, learning, memory, and mood.[37,38] β-ARs are responsive to the endogenous catecholamines (epinephrine and norepinephrine) and the synthetic nonselective β-AR agonist, isoproterenol.

Received February 8, 2013; Revised May 20, 2013; Accepted May 29, 2013.
This work was done at Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
Supported by grants from the National Institutes of Health (RO1-MH51246 and UL 1RR025747).
Authors declare no potential conflicts of interest relevant to this article.
Address reprint requests to Susan S. Girdler, PhD, University of North Carolina at Chapel Hill, CB#7175, Medical School Wing D, Chapel Hill, NC 27599-7175. E-mail: susan_girdler@med.unc.edu
1526-5900/$36.00

http://dx.doi.org/10.1016/j.jpain.2013.05.014

Activation of G protein–coupled transmembrane β-ARs induces signal transduction across the plasma membrane, leading to the activation of adenylyl cyclase and production of the second messenger, cyclic adenosine monophosphate.[37]

Relevance of β-ARs to MRMDs is suggested by several lines of evidence. First, women with an MRMD have blunted blood pressure (BP), heart rate (HR), and cardiac output reactivity to mental stress relative to non-MRMD women,[25,26,46] a pattern consistent with diagnosis-related differences in β-AR mechanisms. Second, estrogen and progesterone, which are pathophysiologically relevant in MRMDs,[64] modulate the activity and expression of β-ARs in animal models.[22,36,53] In humans, greater lymphocytic β_2-AR density is evident in the luteal phase relative to the follicular phase of the menstrual cycle.[75] Third, the clinical relevance of β-ARs to MRMDs was suggested by the findings of Gurguis and colleagues,[31] who observed greater β_2-AR density in PMDD relative to non-PMDD women. Furthermore, in that study, greater β_2-AR binding predicted greater premenstrual symptom severity. We previously demonstrated that only for women with PMDD, but not for non-PMDD controls, was a history of abuse associated with greater β-AR responsivity to isoproterenol, suggesting a role of adverse environmental factors on β-AR mechanisms in PMDD.[27] Fourth, selective serotonin reuptake inhibitors, the first-line therapy for MRMDs,[72] decrease the cortical density of β-ARs.[6,66] This may explain why treatment with propranolol, a centrally and peripherally acting β-AR blocker, has been shown to be effective in ameliorating emotional and physical symptoms of an MRMD.[15]

β-ARs are also implicated in the modulation of pain sensitivity.[7,20,41,61] It is well established that MRMD patients are more sensitive to experimental pain[8,21,46,49,50,74] and suffer from greater clinical pain severity,[1,2,12,39,40,51,77] relative to women without MRMD. In women with chronic pain syndromes (fibromyalgia and temporomandibular disorder), β-AR blockade with propranolol reduces the number of painful body sites and total clinical pain severity, suggesting that β-ARs contribute to real-life clinical pain.[52]

Consequently, one aim of this study was to evaluate in vivo β-AR responsivity as a function of MRMD status. In line with previous in vitro research,[31] we predicted greater β-AR responsivity in MRMD women relative to non-MRMD controls. Our second aim was to investigate the impact of β-AR blockade with propranolol on cardiovascular reactivity to stress and on experimental and clinical pain sensitivity in MRMD and non-MRMD women. We hypothesized that β-AR blockade would eliminate diagnosis-related differences in cardiovascular stress reactivity and would result in the greatest reductions in pain sensitivity in women with an MRMD because of their greater baseline β-AR responsivity and pain sensitivity. Finally, in exploratory analyses, we examined the relationship of β-AR responsivity to pain sensitivity.

Methods

Subjects

Women were recruited from Chapel Hill, NC, and the surrounding area via newspaper, radio, or posted advertisements targeting women with severe premenstrual symptoms (MRMD women) or women without premenstrual symptoms (non-MRMD women). After confirming MRMD status (see below), women were invited for a diagnostic visit, during which they were assessed by a trained interviewer for medical histories and for current and past Axis I psychiatric disorders according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–Text revision* (DSM-IV-TR)[13] using the Mini International Neuropsychiatric Interview.[67] Women were included in the study if they were in good health without current chronic medical conditions, including cardiovascular disorders, acute or chronic pain disorders, and current DSM-IV Axis I psychiatric disorders. Women were not included in the propranolol challenge procedure if they had resting systolic BP <100 mm Hg and/or resting HR <65 beats per minute (bpm) and/or self-reported history of any respiratory or bronchospastic disease, including asthma, obstructive pulmonary disease, and/or anaphylactic reaction to allergens due to contraindications with propranolol.

The study protocol was approved by the University of North Carolina at Chapel Hill Committee on the Protection of the Rights of Human Subjects. Each subject provided written informed consent before participation and received $400 compensation for completion of the entire study protocol.

Procedures

Confirming MRMD Diagnosis

MRMD and non-MRMD status was confirmed prospectively using the Daily Record of Severity of Problems[18] that all women completed daily for 2 or 3 menstrual cycles. Forms were mailed back weekly in order to discourage retrospective reporting. The Daily Record of Severity of Problems consists of 21 items and allows for the quantification of the severity of physical, emotional, and behavioral symptoms of MRMD using a 6-point scale (1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = severe, and 6 = extreme). To classify participants as having MRMD, each met the following criteria: 1) at least a 30% decrease in emotional symptom severity between the 7 luteal-phase days preceding menses compared with follicular-phase days 4 to 10; 2) a rating of emotional symptoms as moderate, severe, or extreme on at least 2 of the 7 premenstrual days; 3) remission of symptoms shortly after the onset of menses followed by a clear symptom-free period (≥6 consecutive days) during the early-to-midfollicular phase; and 4) criteria 1 to 3 were met in at least 2 menstrual cycles.[18,63]

Non-MRMD women met the following criteria: 1) no more than minimal emotional symptoms occurring on fewer than 3 days during the premenstrual week; 2) less than a 30% decrease in emotional symptom severity