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Brief Report

An Unusual Reaction to Opioid Blockade with Naltrexone in a Case of Post-Traumatic Stress Disorder

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An unusual behavioral and cardiovascular reaction was observed during opioid blockade with naltrexone in a 32-year-old male who met DSM III-R criteria for post-traumatic stress disorder (PTSD). As part of an ongoing placebo-controlled investigation of the effects of naltrexone on laboratory and ambulatory blood pressure reactivity, this participant reported experiencing feelings of rage, explosive behavior, and other unpleasant symptoms. When compared to all other subjects (N = 24), this individual showed significantly greater effects of naltrexone on blood pressure reactivity during the laboratory stressor. His ambulatory blood pressures, when compared to placebo, were significantly increased during the 24-hr period following naltrexone. The unusual behavioral and cardiovascular responses following ingestion of naltrexone suggest an important role for endogenous opioids in adjustment to stress in this case of PTSD.

KEY WORDS: post-traumatic stress disorder; endogenous opioids; ambulatory blood pressure; naltrexone; laboratory stress.

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INTRODUCTION

Post-traumatic stress disorder (PTSD) is a psychophysiological disturbance that may arise following exposure to a traumatic event outside the range of usual human experience (American Psychiatric Association, 1987). Some of the characteristic symptoms of PTSD include, among others, reexperiencing the traumatic event(s), numbing of general responsiveness, periodic outbursts of anger, and increased arousal. Endogenous opioid peptides are released during intense stimulation and may be important in acute and chronic adaptation to traumatic stress (McCubbin, 1993). Van der Kolk and colleagues (1985) suggest that these neuropeptide systems may play a role in the development and maintenance of some of the characteristic symptoms of PTSD.

Evidence of opioidergic mechanisms in PTSD derive from several lines of research. For example, animal studies indicate that inescapable stress produces several symptoms that resemble the pathologic profile of PTSD, including analgesia, hyperarousal, and decreased motivation (Van der Kolk *et al.*, 1985). Moreover, pharmacologic blockade of endogenous opioid receptors prevents stress-induced analgesia as well as the performance deficits that typically follow exposure to inescapable stress in rats (McCubbin *et al.*, 1984). Similar effects have been observed in normal human subjects experiencing a perceived uncontrollable stressor (Bandura *et al.*, 1988). Recently, the link between opioids and PTSD has been more directly examined by administration of naloxone to combat veterans with PTSD (Pitman *et al.*, 1990). Combat veterans with PTSD showed decreased pain sensitivity following exposure to a dramatized combat movie. These analgesic effects were blocked with the short-term opioid antagonist naloxone, supporting the notion that endogenous opioids may be directly involved in the expression of PTSD symptomatology.

Our laboratory has been systematically examining the role of opioids in the expression of individual differences in circulatory, neuroendocrine, and behavioral reactivity to stress in young adults (McCubbin *et al.*, 1985; McCubbin *et al.*, 1989). Using pharmacologic blockade of endogenous opioids with naloxone, these studies have suggested that opioids can inhibit cardiovascular, sympathoadrenomedullary, and pituitary–adrenocortical reactivity, and moreover, this opioidergic inhibitory mechanism is diminished in persons at risk for cardiovascular disease. This research has recently been expanded to studies of the effect of the long-lasting oral opioid antagonist, naltrexone, on laboratory reactivity (McCubbin *et al.*, 1992) and 24-hr ambulatory blood pressure patterns. We now report a case of an unusual behavioral and cardiovascular reaction during opioid blockade with naltrexone in a young adult male with a history of childhood abuse and military combat trauma who met DSM III-R criteria for PTSD.

METHODS

The present case study resulted from a reaction to opioid blockade in one individual participating in a single-blind placebo-controlled investigation of laboratory and ambulatory stress. Twenty-four subjects with mildly elevated blood pressures were recruited from an on-campus screening similar to that described in McCubbin *et al.* (1985). Male young adult volunteers with stable mean arterial pressures in the upper quintile of the distribution were scheduled for four in-laboratory psychological stress tests. Because of a related interest in ambulatory pressures, the long lasting, oral opioid blocking drug naltrexone (Trexan, DuPont) was used. In the laboratory, subjects were fitted with an automated blood pressure cuff (Critikon, Tampa), and following a 10-min rest, blood pressures and heart rates were obtained. Subjects were then given either a 50 mg naltrexone tablet or a placebo (order was counterbalanced). Subjects rested for one hour and were then reinstrumented for blood pressure measurement. After a 10-min postdrug rest, participants then performed a difficult ten-minute arithmetic task (McCubbin *et al.*, 1992), followed by a post stress recovery period. After the in-lab study, subjects were equipped with a Spacelabs 90202 ambulatory blood pressure monitor (Spacelabs Inc., Redmond, WA) and a diary for a 24-hr study during normal activity. Drug or placebo within-subject control experiments were scheduled about a week later. The protocol was approved by the University of Kentucky Medical Institutional Review Board and participants gave informed consent for the experimental protocol.

RESULTS

A 32-year-old male (Mr. B) reported an unusual set of reactions following his second laboratory session, during which he had blindly received an oral 50 mg naltrexone tablet. Mr. B had received a placebo tablet during his initial visit to the laboratory, and that laboratory and ambulatory experience was unremarkable. Approximately one week later, Mr. B returned to the laboratory, received 50 mg naltrexone at 2:30 pm, and participated in the laboratory session. At about 4:15 pm, Mr. B was instrumented for ambulatory monitoring, requested to record his activities and to return the equipment 24 hr later. Upon return to the laboratory the following day, Mr. B indicated that he had experienced some unusual symptoms. He was then referred for extended debriefing and psychological evaluation.

The following events and symptoms were reported by Mr. B during debriefing. Approximately 2 hr after administration of naltrexone, Mr. B left the laboratory and drove to visit his wife at a local business where they were both employed. On the way, he reported becoming aware that he was getting a headache and felt that something was "not quite right" with his visual perception. The onset of these symptoms was reported to be gradual.

Upon arrival, he told his wife about his symptoms. As he was looking at her, he felt he was losing his depth perception; that is, he experienced the image of his wife as two-dimensional, like "an image on a mirror." He also experienced the image of his wife as somewhat distorted, which he described as similar to looking through a "carnival mirror." Furthermore, he noted difficulties focusing, and that his vision appeared to be "skewed" to his right. According to Mr. B, his wife was amused by the explanation of his symptoms and began to jokingly move her head from side to side. This made him "very upset" and as a result he "grabbed" her and told her "don't do that anymore." Subsequently, he noticed the owner watching him "with a strange look." Mr. B then became angrier and accused his wife of not caring that he had a headache and not "paying attention" to him. At that point, he angrily knocked down several boxes. He then noticed his headache was dissipating and his visual distortions had disappeared though he remained angry. His wife proceeded back to the stockroom where he followed her while enraged "at her behavior." Shortly after, he returned to the front of the store attempting to understand the source of his rage when he observed his ambulatory blood pressure cuff on the floor. He believes he took it off and dropped it while arguing with his wife. Subsequently, he left the store, sat in his car, and replaced his blood pressure cuff. While in the car, he noted that his anger was "turned off like a faucet." He then returned home and reported no further sequelae.

Mr. B indicated that his behavior had been "very mean, yelling and screaming past the point of rage." He denied other incidents of similar behavior without significant provocation. He later reported that his angry response was totally out of proportion to what had occurred. Furthermore, he perceived his reaction as a loss of control which was both unfamiliar and disturbing. Mr. B denied taking alcohol or other drugs. He attributed his symptoms and his behavior to possible intake of naltrexone.

Case History and Diagnosis

Mr. B was reportedly diagnosed with dyslexia during the second grade, placed in special education classes, and was prescribed Valium for "hyperactivity." He reported that he and his 2 siblings were repeatedly

physically abused in childhood, including beatings, being locked in a closet for extended periods, and threats to his life. He reported suicidal ideation following these experiences.

Mr. B enlisted in the Army following his high school graduation and remained in active service until shortly after his participation in a combat mission. He indicated that during the mission he was almost shot and that he killed one person to save a friend. He said that he had not resolved his own feelings about having taken someone's life.

Mr. B met the DSM-III-R (American Psychiatric Association, 1987) criteria for the diagnosis of PTSD. His history of parental abuse, and his experiences in combat represent events that are, in our judgment, outside the range of normal human experience. He presented with the following symptoms: persistent arousal, hypervigilance, intrusive recollections and nightmares, exaggerated startle responses to innocuous environmental stimuli, avoidance of thoughts associated with his traumas, difficulty remembering aspects of these events, identification with other victims of trauma, detachment from significant others, and a sense of foreshortened future.

Cardiovascular Data

Mr. B's resting diastolic pressures in the laboratory prior to administration of naltrexone were not significantly different from the group average (Mr. B = 73.6 mm Hg versus group mean = 75 ± 3.41 SD). In contrast, however, his resting in-lab systolic pressure was significantly lower than the group average (Mr. B = 108 mm Hg versus group average 123.2 ± 7.25 , $z = 2.10$, $p < 0.05$). Mr. B's blood pressure responses to arithmetic stress were not different from the group average following placebo administration.

Administration of naltrexone did not significantly affect his resting pressures in the laboratory. However, naltrexone produced increases in blood pressure reactivity during and after stress and these effects were significantly greater than the group averages. For example, the drug effect on Mr. B's diastolic reactivity was significantly greater than the group average in the second 5 minute block of arithmetic stress ($z = 2.53$, $p < 0.025$) and during both the first ($z = 3.04$, $p = 0.0025$) and second ($z = 2.23$, $p < 0.05$) five-minute blocks of recovery from stress. Naltrexone also increased Mr. B's ambulatory blood pressures during the 24-hr period immediately following his laboratory sessions. For example, his 24-hr average ambulatory blood pressures were 123/73 mm Hg following placebo, and

130/80 following naltrexone ($t(36) = 5.83, p < 0.001$ for systolic, $t(36) = 6.21, p < 0.001$ for diastolic). There were also effects of naltrexone on acute ambulatory pressor responses. While there were no systolic readings above 140 mm Hg during the placebo period, 22.7% of systolic readings were above 140 mm Hg during the naltrexone period. For ambulatory diastolic pressures, 6.7% of readings were above 90 mm Hg during the placebo period, but 18.2% of diastolic readings were above 90 mm Hg during the naltrexone period.

DISCUSSION

The present case study demonstrates an unusual reaction to pharmacologic blockade of opioid receptors with naltrexone in a case of post-traumatic stress disorder. Data from an extensive clinical evaluation indicates that Mr. B clearly met the DSM III-R criteria for PTSD and he acknowledged this diagnosis. He added that he had not previously sought treatment of his disorder for fear of being stigmatized and had underreported the severity of his symptoms to military personnel and to counselors.

If endogenous opioids are important in adaptation to repeated trauma, then it is possible that blockade of these adaptive mechanisms could precipitate significant psychological distress. In the present case, naltrexone administration evoked hypervigilance and anger outbursts, both of these symptoms are included in the DSM-III-R (American Psychiatric Press, 1987) criteria for PTSD. The relationship between opioids and other unusual symptoms such as dissociative phenomena requires further investigation. Mr. B's reported history of developmental hyperactivity and dyslexia could not be confirmed. It remains unknown whether the history of these disorders contributed to Mr. B's reaction to naltrexone.

Some of the symptoms of PTSD may reflect underlying psychobiologic mechanisms similar to exogenous opiate withdrawal phenomena (Van der Kolk *et al.*, 1985). Pharmacologic opioid blockade can precipitate withdrawal in opiate dependency, and the present case could reflect similar endogenous phenomena. Exaggerated blood pressure reactivity is also typical of opiate withdrawal, further strengthening the conceptual similarities between the present results, exogenous opiate withdrawal, and PTSD. Moreover, the antihypertensive medication clonidine eases opiate withdrawal symptoms and may also be effective in treatment of PTSD hyperreactivity (Gold *et al.*, 1978; Kolb *et al.*, 1984).

While the present case study results cannot be definitively ascribed to administration of naltrexone, both the blood pressure and behavioral responses following ingestion of naltrexone are consistent with a role of endogenous opioids in acute and chronic adjustment to stress in this case of PTSD. Therefore, more research is needed on the role of endogenous opioids in PTSD, but it is also recommended that opioid receptor blockade, especially with naltrexone, be utilized with caution in persons with a history of trauma.

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