HYPNOTIC RELAXATION THERAPY FOR REDUCTION OF HOT FLASHES IN POSTMENOPAUSAL WOMEN: Examination of Cortisol as a Potential Mediator

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Abstract: Hypnotic relaxation therapy (HRT) has been shown to reduce hot flashes in postmenopausal women and breast cancer survivors. While the biological mechanism by which HRT reduces hot flashes is unknown, it has been speculated that reduction of stress mediates the intervention’s effectiveness. The purpose of the present study was to examine the effect of HRT on a known biomarker of stress (cortisol) and changes in cortisol as a mediator. Sixty-two postmenopausal women received hypnotic relaxation therapy for hot flashes and completed measures of hot flashes in addition to providing cortisol samples at baseline and endpoint. HRT resulted in significantly decreased early evening salivary cortisol concentrations. However, changes in salivary cortisol concentrations did not mediate the effects of HRT.

Vasomotor symptoms (hot flashes and night sweats) pose a major burden upon postmenopausal women. The subjective sensation of heat arising from the head and upper chest (Boekhout, Beijnen, & Schellens, 2006) is often accompanied by perspiration, anxiety, irritability, and distress (Finck, Barton, Loprinzi, Quella, & Sloan, 1998). In addition, hot flashes can negatively impact mood, sleep, and sexual functioning, resulting in an associated decreased quality of life (Carpenter et al., 1998; Kronenberg, 1994; Williams, Levine, Kalilani, Lewis, & Clark,

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Despite the significant problem of hot flashes, treatment options have been limited due to concerns over health risks associated with hormone therapies and undesirable side effects of antidepressant pharmacotherapies (e.g., Pandya et al., 2005; Rossouw et al., 2002; Stearns et al., 2005; Suvanto-Luuukkanen et al., 2005).

Hypnotic relaxation therapy (HRT) is a mind-body intervention that has been demonstrated efficacious in the reduction of hot flashes among postmenopausal women and breast cancer survivors (Elkins, Fisher, Johnson, Carpenter, & Keith, 2013; Elkins et al., 2008). Data from our large (N = 187) main clinical trial (Elkins et al., 2013) examining the effect of hypnosis upon hot flashes in postmenopausal women showed that, from baseline to endpoint, postmenopausal women randomized to a 5-week hypnotic relaxation intervention experienced, on average, a 63.87% reduction in self-reported hot flashes in comparison to a 9.24% reduction among structured attention controls (p < .001). These reductions persisted at 12-week follow-up and women randomized to the hypnosis intervention reported, on average, a 74.16% reduction in weekly hot flashes in comparison to a 17.13% reduction among structured attention participants (p < .001). In addition, at 12-week-follow-up, physiologically measured hot flashes were reduced by 56.86% among participants randomized to the hypnosis intervention but only by 9.94% among structured attention participants (p < .001). Further, hot-flash-related daily interference (p < .001) and hot flash score (p < .001) were also significantly improved in comparison to controls.

Currently, the exact physiological mechanism by which HRT reduces vasomotor events has yet to be identified; however, it is possible that the effects produced by the intervention may result from alterations of physiological responses to psychological stress, a documented trigger for hot flashes (Carpenter, Johnson, Wagner, & Andrykowski, 2002; Kronenberg, 1990). Cortisol is a well-known biomarker of the stress response and an index of hypothalamic-pituitary-adrenal (HPA) axis activation (Mello, 2008). The purpose of the present study was twofold: (a) to test the hypothesis that hypnotic relaxation therapy would result in decreased levels of a known biomarker of the stress response (i.e., cortisol) and (b) to examine changes in cortisol as a mediator in the reduction of self-reported hot flashes, physiologically measured hot flashes, hot flash score, and hot-flash-related daily interference in postmenopausal women following a 5-week HRT intervention.

**Methodology**

Details explaining the rationale and methods of the main study examining hypnosis’ effects upon hot flashes in postmenopausal women have been described elsewhere (Elkins et al., 2013). The
following provides information regarding the methodology relevant to this secondary study and article.

Participants

Participants were postmenopausal women who were experiencing a minimum of seven daily (50 weekly) hot flashes at baseline. Eligible participants were age 18 or greater, had not had a menstrual period for at least 12 months or had not had a menstrual period for at least 6 months and had (a) a history of surgical bilateral oophorectomy or (b) medically documented levels of follicle stimulating hormone (FSH) of 40 mIU/ml. Participants were also required to discontinue hormone replacement therapy for hot flashes and to go through a washout period. Exclusionary criteria included receipt of other hot flash treatment or utilization of any complementary and alternative medicine methods for hot flashes. In addition, persons with a psychiatric history that included borderline personality disorder, psychosis, or other significant psychopathology were excluded from the study as such conditions are contraindicated with clinical hypnotherapy treatment (Elkins, 2013). All participants completed a written informed consent, and all aspects of the study were carried out with the approval of the university’s institutional review board.

Hypnotic Relaxation Therapy

Sixty-two women underwent five weekly sessions of hypnotic relaxation therapy for hot flashes. The hypnotic relaxation therapy intervention was delivered individually, according to a treatment manual, and by hypnotherapists with training in the intervention (Elkins, 2013; Elkins & Hammond, 1998). The intervention consisted of an initial induction followed by suggestions specific to the goals of reducing hot flashes. In addition, participants were provided with an audio recording for use in guided, at-home practice, and they were instructed in self-hypnosis practice.

Measures

Hot Flash Symptoms Diary (HFSD). The Hot Flash Symptoms Diary (Sloan et al., 2001) was utilized to measure hot flash frequency. The diary allows for recording of hot flash frequency and severity (mild, moderate, severe, and very severe) over a 7-day period. The instrument also enables calculation of hot flash score (product of frequency × severity). Participants completed hot flash diaries prior to Session 1 (baseline) and following the completion of five sessions (endpoint).
**Biolog™ skin conductance monitor.** The Biolog™ ambulatory recorder (UFI Model 7-day 3991 SCL, Morro Bay, CA), a sternal skin conductance monitor, was used for the physiological measure of hot flashes. Ambulatory skin conductance monitoring is commonly used as a physiological measurement of hot flashes. In accord with current published norms (Freedman, 1989, 1998; Freedman & Krell, 1999; Freedman Norton, Woodward, & Cornelissen, 1995), a hot flash was defined by an increase of 2 μmho of skin conductance within a time frame of 30 seconds. Participants wore the hot flash monitor for a 24-hour period at baseline and at endpoint.

**Salivary cortisol.** Participants used the Salimetrics Oral Swab to collect personal salivary cortisol samples at four separate, specified time frames during the same day during the week before the first session (baseline) and endpoint, following the completion of five sessions (endpoint). Samples were collected during the morning (before breakfast), late morning (before lunch), early evening (before dinner), and evening (after dinner). Participants were instructed to refrigerate (for not more than 24 hours) or to freeze samples within 30 minutes of collection. In addition, in order to control for potential confounds that may influence cortisol measurement, participants were asked to rinse their mouths prior to providing a sample and to abstain from the following: eating a large meal; consuming alcohol; eating dairy, acidic, or sugary foods; or brushing their teeth for a brief period of time prior to data collection. Of the original 93 women who received hypnosis intervention, 77 provided cortisol data and, of these, 62 provided samples at both baseline and endpoint. Thus, these 62 were included in the analysis. Salivary cortisol samples were assayed using a time-resolved immunoassay with a cortisol-biotin conjugate as a tracer, and samples were analyzed in duplicate.

**Hot Flash Daily Related Interference Scale.** The impact of hot flashes on overall quality of life, including nine specific activities (i.e., work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, enjoyment of life) was measured using the Hot Flash Daily Related Interference Scale (Carpenter, 2001). Concurrent validity, sensitivity, and internal consistency (alpha of .96) of the instrument have been established.

**Analytical Method**

A paired-samples t test was conducted for each time point in order to test the hypothesis that hypnotic relaxation therapy would result
in decreased salivary cortisol levels following a 5-week hypnotherapy intervention for hot flashes.

To evaluate whether changes in physiologically recorded hot flashes, self-reported hot flash frequency, hot flash score, or hot-flash-related daily interference were mediated by changes in salivary cortisol, separate models were created to examine mediation effects with each outcome of interest. In accordance with Baron and Kenny (1986), for each model, mediation effects were tested through regressing: (a) the mediator (change in salivary cortisol concentration) upon the independent variable (IV — group assignment); (b) the dependent variable (DV — i.e., change in hot flash frequency, change in hot flash score, change in physiologically measured hot flashes, or change in hot-flash-related daily interference) upon the IV; and (c) the DV upon the mediator and the IV. Establishment of mediation required that, in the first and second equations, the IV affected the mediator and DV, respectively, and that the third equation demonstrated the DV was affected by the mediator. Finally, the DV must have been affected less by the IV when regressed on the IV and mediator simultaneously. In addition, $p$ values were calculated by calculating the product of the path coefficients that comprised the indirect effect, or the effect from the IV, group assignment, to salivary cortisol concentration (the potential mediator) and from the mediator to each outcome of interest, and then dividing that product by the standard error of the product (Baron & Kenny, 1986; Sobel, 1982).

Additionally, in each model, examination of the direct path from the IV to the DV provided insight into the potential for partial or perfect mediation by changes in salivary cortisol concentration. In reporting mediation results, outcomes are reported in a manner consistent with that delineated by Baron and Kenny (1986). That is, the path leading from the IV to the mediator is labeled “$a$,” the path from the mediator to the DV is labeled “$b,$” the path from the IV to the DV is labeled “$c,$” and the path from the IV to the DV, with the mediator controlled, is labeled “$c’.$” The product of the coefficients $a$ and $b$ is labeled “$ab$” and indicates the mediated effect of the IV upon the DV.

Data Screening

Outliers (measuring greater than two standard deviations from the mean) were evaluated through the use of boxplots. Screening of baseline data revealed four outliers for late-morning cortisol concentrations, three for early evening, and four for evening. At endpoint, screening revealed one outlier for morning cortisol and five for evening cortisol concentration. In addition, boxplots revealed four outliers for change in cortisol concentration from baseline to endpoint. For each of these variables, outliers were winsorized to prevent unbalanced influence of these values upon the analysis (Tabachnick & Fidell, 2007).
RESULTS

Details on the primary study flow and outcome analysis are published elsewhere (Elkins et al., 2013). Briefly, the mean age was 54.35 years. Participants were largely white (71%), followed by African American (16.1%), Hispanic (8.1%), Native American (3.2%), and Asian (1.6%). Most participants (59.7%) were married, and 40.3% were divorced, widowed, separated, or single.

Changes in Salivary Cortisol Concentration Following Receipt of Hypnosis

Results indicated that, at the early evening collection time, salivary cortisol concentration significantly decreased from baseline, $M = 0.143$, $SD = 0.132$, to endpoint, $M = 0.105$, $SD = 0.093$, $t(57) = 2.021$, $p = .048$. Otherwise, pre- to postintervention changes in salivary cortisol concentration among participants who had received hypnosis were insignificant (see Figure 1). Because early evening was the only time in which cortisol concentration significantly decreased following the hypnotherapy intervention, change in cortisol concentrations from this time period were explored for possible mediation effects upon the hot flash intervention.

Change in Cortisol as a Mediator in Change in Self-Reported Hot Flash Frequency

Hypnosis’ effect upon change in hot flash frequency was not mediated by change in salivary cortisol (see Figure 2). The direct effect of

![Figure 1](image_url)  
*Figure 1.* Change in cortisol concentration pre- and posthypnosis intervention.
the intervention was significant, $c = .640$, $SE = 4.617$, $p = .00$, resulting in reduced hot flash frequency, even when controlling for change in salivary cortisol, $c' = .636$, $SE = 4.865$, $p = .000$. However, the effect of hypnosis upon change in salivary cortisol concentration was insignificant, $a = -.046$, $SE = 0.097$, $p = .630$, as was the effect of salivary cortisol concentration upon change in hot flash frequency, $b = -.010$, $SE = 4.726$, $p = .894$. Thus, the indirect effect of hypnosis upon change in hot flash frequency by way of change in salivary cortisol concentration, $ab = .0005$, $SE = 0.217$, $p = .998$, was also insignificant.

**Change in Cortisol as a Mediator in Change in Physiologically Measured Hot Flashes**

Changes in pre- to postintervention salivary cortisol concentration did not mediate the effect of hypnosis upon changes in biologically recorded hot flashes from baseline to endpoint (see Figure 3). The direct effect of the hypnosis intervention was again significant, $c = .346$, $SE = 1.198$, $p = .001$, even with changes in salivary cortisol concentration controlled, $c' = .366$, $SE = 1.196$, $p = .001$, thereby resulting in reduced frequency of physiologically recorded hot flashes. However, the hypnosis intervention did not significantly affect changes in salivary
cortisol concentrations from baseline to endpoint, $a = -0.046, SE = 0.097, \, p = .630$. Nor did changes in salivary cortisol from pre-to postintervention account for the effect of the hypnosis intervention upon physiologically measured hot flashes, $b = .018, SE = 1.050, \, p = .866$. The indirect effect of hypnosis by way of change in salivary cortisol was also insignificant, $ab = .0008, SE = 0.048, \, p = .986$.

**Cortisol Change as a Mediator in Change in Hot Flash Score**

The effect of hypnosis upon pre- to postchange in hot flash score was not mediated by pre- to postintervention changes in salivary cortisol concentration (see Figure 4). The hypnosis intervention significantly affected changes in hot flash score from baseline to endpoint, $c = .608, SE = 1.799, \, p = .000$. That effect held, $c' = .617, SE = 1.877, \, p = .000$, even when controlling for the effect of changes in salivary cortisol concentration, $b = -.018, SE = 1.823, \, p = .810$. Further, the effect of hypnosis upon change in salivary cortisol concentration was insignificant, $a = -.046, SE = 0.097, \, p = .630$, as was the indirect effect of the hypnotherapy intervention upon hot flash score via salivary cortisol changes, $ab = .0008, SE = 0.084, \, p = .992$. 

*Figure 3. Change in cortisol as a mediator of change in physiologically measured hot flashes.*
Cortisol Change as a Mediator in Change in Hot-Flash-Related Daily Interference

Changes in cortisol concentration from baseline to endpoint did not mediate the intervention’s effect upon changes in hot-flash-related daily interference (see Figure 5). The effect of the hypnosis intervention upon changes in hot-flash-related daily interference was significant, \( c = .548, SE = 0.382, p = .000 \), and this effect was not accounted for by the effect of changes in cortisol concentration, \( c’ = .549, SE = 0.395, p = .000 \). Further, the hypnotherapy intervention did not significantly affect changes in cortisol concentration from baseline to endpoint, \( a = -0.046, SE = 0.097, p = .630 \). Nor did changes in cortisol affect change in hot-flash-related daily interference from baseline to endpoint, \( b = .000, SE = 0.384, p = .999 \). Thus, the indirect effect of hypnosis upon changes in hot-flash-related daily interference through changes in cortisol concentration was, not surprisingly, insignificant, \( ab = .000, SE = 0.017, p = 1.00 \).

Discussion and Conclusions

The present study was designed (a) to test the hypothesis that hypnotic relaxation therapy would result in decreased levels of a known
biomarker of the stress response (i.e., cortisol) and (b) to examine changes in cortisol as a mediator in the reduction of hot flashes and hot-flash-related daily interference in postmenopausal women. Specifically, we investigated changes in pre- and postintervention salivary cortisol following the hypnotic relaxation therapy intervention as well as the indirect effects of the intervention upon pre- to postintervention changes in self-reported hot flash frequency, physiologically recorded hot flashes, hot flash score, and hot-flash-related daily interference.

Following 5 weeks of hypnotic relaxation therapy, outcomes showed a significant decrease in pre- to postintervention, early evening cortisol concentrations. This is consistent with the hypothesis that hypnotic relaxation therapy ameliorates stress. However, for each of the proposed mediation models, while the direct effect of the hypnotherapy intervention upon the outcome variables of interest was significant, the indirect effect, via changes in early evening salivary cortisol concentration, was not. Thus, change in pre- to postintervention cortisol levels did not mediate the effects of HRT upon hot flashes (self-reported frequency, hot flash scores, physiologically measured hot flashes) or hot flash daily interference.
Research has not yet determined the mechanism underlying the effects of hypnotic relaxation or the pathway through which HRT exerts its effects upon hot flashes. Further, the pathophysiology of hot flashes is complex and poorly understood. Hot flashes are believed to be related to a functional disruption of the thermoregulatory zone in the hypothalamus (Freedman, 2000, 2001; Rossmanith & Ruebberdt, 2009). Although several theories that implicate a number of physiological variables (e.g., Berendsen, 2000; Charkoudian, 2003; Dormire; 2009; Dormire & Reame, 2003) have been proposed, sympathetic autonomic reactivity has most often been hypothesized due to associated symptoms such as increased heart rate and sweating (Sood et al., 2013); however, others have suggested that decreased parasympathetic, rather than increased sympathetic, involvement may play a larger role (Thurston, Christie, & Matthews, 2010).

Thus, examination of hypnosis’ effects upon epinephrine, norepinephrine, and acetylcholine may be a focus of future research. In addition, research has given an indication of a relationship between anxiety and depression and hot flashes (e.g., Bromberger et al., 2013). For example, data have demonstrated an association between anxiety and depression and hot flash occurrence (Juang, Wang, Lu, Lee, & Fuh, 2005), and anxiety has been associated with hot flash frequency and severity (Lerman et al., 2011) and has even been shown to be predictive of hot flashes (Freeman et al., 2005). Moreover, a number of trials have demonstrated the efficacy of antidepressants in the treatment of hot flashes (e.g., Loprinzi et al., 2002; Stearns, Beebe, Iyengar, & Dube, 2003; Nelson et al., 2006). Notably, the mechanism by which antidepressants reduce hot flashes is not fully understood; however, it is assumed that the neurotransmitters serotonin, dopamine, or norepinephrine may be involved (Loprinzi et al., 2002). Given that hypnotherapy has been shown to result in a reduction of depressive and anxious symptoms (e.g., Lioissi & White, 2001; Saadat et al., 2006), it is possible that hypnotherapy may exert its effects on hot flashes through these neurotransmitters and merits further investigation to examine these possibilities.

In addition, several considerations are worthy of note. First, salivary cortisol can be affected by variances in day-to-day occurrences (e.g., stressful situations, exercise, etc.), and these factors should be examined in future studies. Second, recent research has indicated that the varied neural networks that influence HPA activity may also influence salivary cortisol; thus, a linear relationship between serum and urinary cortisol cannot be assumed (Hellhammer, Wüst, & Kudielka, 2009). Hypnosis clearly affects the subjective perception of and the physiologically measured occurrence of hot flashes and ameliorates stress. Although it follows that one possible mechanism through which hypnosis may exert its effects is through reducing physiological reactivity
to stress, findings of this study challenge the hypothesis that hypnosis exerts its effects upon hot flashes via modulation of HPA reactivity to stress. Additional study of the potential role of stress in reducing hot flashes is, therefore, warranted.

In sum, although hypnotherapeutic intervention can significantly and positively impact postmenopausal hot flashes, much remains unknown. The outcomes of the present study suggest that alterations in HPA response to stress may not be a mediating factor in hypnosis' effects. However, functions and alterations of the stress response may be better evaluated through examination of physiological variables of interest immediately preceding or following the hypnotic induction, and this has yet to be investigated. Further, hypnosis may reduce hot flashes through the influence upon other physiological variables that have yet to be determined. Understanding these factors and the manner in which hypnotic relaxation therapy reduces hot flashes is critically important to both establishing effective treatments for hot flashes and to effective application of hypnotic relaxation therapy.

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References


Hypnotische Entspannungstherapie zur Reduktion von Hitzewallungen bei postmenopausalen Frauen: Die Untersuchung von Cortisol als möglichen Bahner

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L'hypnorelaxation pour la réduction des bouffées de chaleur chez les femmes postménopausées: Étude du cortisol en tant que médiateur possible

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Résumé: Il a été démontré que l'hypnorelaxation (HR) réduit les bouffées de chaleur chez les femmes ménopausées et chez celles qui ont souffert d'un cancer du sein. Le mécanisme biologique qui permet la réduction des bouffées de chaleur dans la thérapie RH n'est pas connu, mais l'on pense que la réduction du stress médie l'efficacité de la thérapie. L'objet de la présente étude consiste à examiner l'effet de la thérapie RH sur un marqueur biologique connu du stress (le cortisol) ainsi que les changements dans le cortisol utilisé en tant que médiateur. Soixante-deux femmes ménopausées ont suivi une thérapie RH et ont évalué leurs bouffées de chaleur en plus de fournir des échantillons de cortisol prélevés avant et après la thérapie. La thérapie RH a donné lieu à une baisse importante des concentrations de cortisol salivaire au début de la soirée. Toutefois, les changements dans les concentrations de cortisol salivaire n'ont pas médié l'effet de la thérapie RH.

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Terapia hipnótica de relajación para la reducción de bochornos en mujeres posmenopáusicas: Evaluación del cortisol como un mediador potencial

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Resumen: Se ha demostrado que la terapia hipnótica de relajación (THR) reduce los bochornos en mujeres posmenopáusicas y en sobrevivientes de cáncer de mama. A pesar de que no se conoce el mecanismo biológico por medio del cual la THR reduce los bochornos, se ha especulado que la reducción del estrés media la eficacia de la intervención. El propósito del presente estudio fue examinar el efecto de la THR en un biomarcador conocido del estrés (el cortisol) y los cambios en el cortisol como un mediador. Sesenta y dos mujeres posmenopáusicas recibieron terapia hipnótica de relajación para los bochornos, completaron mediciones sobre sus bochornos, y proporcionaron muestras de cortisol en línea basal y al final. La THR resultó en un decremento significativo en la concentración de cortisol en saliva temprano por la tarde. Sin embargo, los cambios en la concentración de cortisol en saliva no medieron los efectos de la THR.

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