Title
Hormonal control in a state of decreased activation: Potentiation of arginine vasopressin secretion

Journal
Physiology & Behavior, 35(4)

ISSN
0031-9384

Authors
O'Halloran, JP
Jevning, R
Wilson, AF
et al.

Publication Date
1985-10-01

DOI
10.1016/0031-9384(85)90146-5

Physiology & Behavior, Vol 35, pp 591–595 Copyright © Pergamon Press Ltd., 1985 Printed in the U S.A. 0031-9384/85 $3.00 + 00

Hormonal Control in a State of Decreased Activation: Potentiation of Arginine Vasopressin Secretion

J. P. O'HALLORAN,†R. JEVNING, *[1] A. F. WILSON,* R. SKOWSKY,‡
R. N. WALSH† AND C. ALEXANDER§

Departments of Medicine and Physiology and School of Social Sciences,† University of California, Irvine Irvine, CA 92717*
Department of Endocrinology,‡ Long Beach Veteran's Administration Hospital, Long Beach, CA 90822 and Departments of Psychology and Social Relations,§ Harvard University, Cambridge, MA 02138

Received 24 May 1984

O'HALLORAN, J. P., R JEVNING, A. F WILSON, R. SKOWSKY, R. N. WALSH AND C. ALEXANDER. *Hormonal control in a state of decreased activation Potentiation of arginine vasopressin secretion.* PHYSIOL BEHAV 35(4) 591–595, 1985 —Behaviorally induced stress is associated with increased arginine vasopressin (AVP) secretion. In this report we describe a phasic conditioned response of AVP secretion yielding 2.6–7.1 times normal plasma concentration of this hormone in association with a physiological state of *decreased* activation, that associated with the mental technique of "transcendental meditation" (TM) in long-term practitioners (6–8 years of regular elicitation) Such a very large phasic response of AVP was previously unknown in the normal physiology of AVP. This elevation was not accompanied by elevation of plasma osmolality. Unstylized ordinary eyes closed rest in a separate group of subjects studied in the same manner was associated with normal plasma AVP concentration. Galvanic skin resistance (GSR) increased during both TM and rest with significantly larger increase associated with TM. Other measures of activation, including muscle metabolism, and the Spielberger Anxiety Inventory indicated marked relaxation in association with TM. In previous research it has been shown that blood pressure does not change acutely during this behavior. These observations indicate that neither stress nor operation of other usual homeostatic control mechanisms are responsible for elevated for AVP in the meditators. It is speculated that the apparently unique mechanism of TM-induced AVP secretion may be more specifically related to the behavioral effects of meditation.

Hormones Meditation Consciousness Hypometabolism TM

ARGININE vasopressin (AVP) is a nonapeptide which is synthesized within the central nervous system in medial hypothalamic nuclei. It is axonally transported to various brain regions including ependymal cells lining the third ventricle as well as to the posterior lobe of the pituitary gland from where it is secreted into the systemic circulation. Well established physiologic actions of AVP include regulation of total body fluids, blood volume and vasoconstrictor effects on the smooth muscle of the vascular system [25]. Although the mechanisms are obscure, recent studies of the effects of peripheral and central administration of exogenous vasopressin and its neurally active analogues in animals and humans suggest involvement in a variety of cognitive processes including learning and memory functions [5, 7, 8] and, more specifically, the acquisition and retention of adaptive behavior patterns [4,8]. Additional reported effects of AVP in humans suggest psychotherapeutic and behavior-modifying properties [9,34] as well as improvement of attentional processes [1]. Implicit in many of these reports is the notion that naturally occurring modification of existing, or acquisition of new behavior patterns may be facilitated by an increase of endogenous AVP activity centrally and/or peripherally. However, except for states of stress, potentiation of AVP secretion associated with behavior modification or adaptation has not been demonstrated.

The purpose of the present study was to determine if long-term, regular practice of the technique of "transcendental meditation" (TM), reported to induce numerous behavioral changes [10, 12, 16, 22, 28], may be associated with altered secretion of AVP. This behavior, elicited twice daily in the morning and evening for 20–40 minute periods by the regular practitioner, is associated with major physiologic changes in long-term subjects [17–19].

METHOD

Twelve subjects, six long-term meditation practitioners (5–10 year instructors of TM) and six non-meditating individuals ("ordinary rest" group), were studied. All subjects were normal, university educated individuals and did not use tobacco, alcohol or regular medication. Their ages ranged

[1]Requests for reprints should be addressed to R. Jevning, Departments of Medicine and Physiology, University of California, Irvine, Irvine, CA 92717.

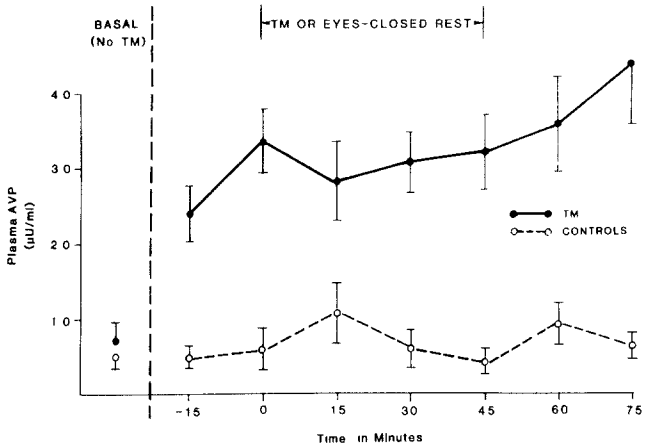

FIG. 1. Plasma concentrations (mean±S E) of AVP for the TM group (●—●) and for the ordinary rest group (○——○) before, during and after an eyes-closed period of either meditation or rest The additional point for the TM group represents the mean pAVP level in samples taken on a different day than the time series samples. These separate samples were taken at a time of day different from the usual time at which these subjects routinely practice TM (12–1 p.m.)

from 22 to 31 years (mean of 26 in both groups). Each group consisted of 4 men and 2 women. The ordinary rest group was composed of individuals who did not practice any form of systematic relaxation nor any meditation technique.

Blood sampling procedures were conducted in a small, semi-soundproof enlcosure and all samples were collected between 9 and 10:30 a.m., a time period approximating the typical time of morning at which these subjects regularly practice meditation. Subjects were familiarized with the laboratory and its personnel on a day previous to the day of the experiment. Written informed consent was obtained from each subject on this occasion.

Arterial (brachial) and venous catheters (1.5 in 20-gauge Longdwell) were inserted into the arms of recumbent subjects following local anesthesia with a 1% lidocaine solution. Electroencephalographic (EEG) and galvanic skin resistance (GSR) leads were also attached. The monopolar EEG was recorded from C_2-left mastoid process with forehead as ground using Grass silver cup electrodes. EEG records from a Grass model 7 polygraph (with low and high half-amplitude filters set at 0.15 and 35 hz, respectively) were scored in 30-sec epochs according to the criteria of Rechstaffen and Kales [24]. GSR measures were derived from 9 mm Ag-AgCl electrodes attached to thenar and hypothenar eminences of the right palm. A Grass DC amplifier was used. GSR data was analyzed by calculating relative fractional differences of resistance values during the eyes-closed period (one minute intervals), compared to the value at the start of the eyes-closed period. After a 2 hours equilibration period to allow any changes associated with catheter placement to be attenuated, subjects were seated in a comfortable chair inside the enclosure. Intravenous extension lines were then attached, allowing blood to be drawn from outside the enclosure without disturbing the subject. Blood samples were drawn through 3-way stepcocks, connected to flexible 36-inch extension lines, kept patent with a heparinized saline solution. To facilitate meditation/relaxation, room lights were dimmed and noise was minimized during the experiment.

Using a time series experimental design [14], blood samples were drawn at 15 minute intervals over a 90 minute period, divided into a 15 minute (eyes-open) pre-meditation/pre-rest period, a 45 minute (eyes-closed) meditation/rest period and a 30 minute (eyes-open) post-meditation/post-rest period For the purpose of assessing psychologic stress each subject completed a Spielberger State-Trait Anxiety Inventory or STAI [33] both before and following the experimental period Forearm oxygen consumption, an indicator of skeletal muscle activity, was also determined and has been reported previously [18]. On a separate day, an additional single blood sample was taken from each meditation subject between 12–1 p m , a time different from their routine meditation practice time.

Blood samples were placed in chilled tubes and serially centrifuged (5°C) at 6000 g for 8 minutes and the separated plasma specimens stored at −70°C until assayed. Plasma arginine vasopressin (pAVP) was quantitated under double-blind conditions using a highly specific radioimmunoassay [31]. Radioimmunoassay characteristics include a sensitivity of 0 2 μU/ml (0.6 pg/ml) and a C.V of 4.8% within assay and 9.6% between assay. The antiserum used (R-71) has negligible crossreactivity with arginine vasotocin (AVT), the ratio of AVT:AVP at 50% binding is 350:3, and oxytocin did not exhibit any significant cross reaction with labelled antigen

RESULTS

pAVP concentrations (mean±S E.) for both groups are shown in Fig. 1. Initial mean AVP concentration of the TM group was approximately 5 times that of the rest group; mean values for the meditation group ranged from 2.6 to 7.1 times the corresponding mean values for the rest group throughout the experiment. Of the 42 individual data points in each group, there was complete separation of AVP concentration between groups except at one point. Mean AVP levels were significantly different between rest and TM groups in the ANOVA ($p<0.001$). Regression coefficients of AVP change over time also differed significantly between groups ($p<0.05$) with a linear increase characterizing the TM group. Mean pAVP values for the rest group were within the normal range for measurements in this laboratory on healthy subjects (0.75±0.50 μU/ml; [31]). pAVP levels in the single, separate samples drawn at a different time of day from those of the time series experiment were also within the normal range in meditation subjects.

Plasma osmolality values for both groups were within the range of values for normal ambulatory subjects (289±5; [24,31]). Plasma osmolality did not vary significantly over time for either group, nor was there any significant difference between groups at any time point.

Scores on the STAI were significantly lower for the meditation group compared to the rest group both before and following the sampling period for both "A-state" and "A-trait" anxiety indices (Table 1). There was no significant change of STAI scores over the course of the sampling period for either group. Initial GSR values (taken at the start of the eyes closed, meditation/relaxation period) showed no significant difference between subject groups. Both groups showed significant increase of GSR levels (Fig. 2) over the duration of the eyes-closed meditation/relaxation period with a significantly larger increase ($p<0.01$) associated with TM. Forearm respiration (mostly due to muscle) declined mark-

TABLE 1

SPIELBERGER STATE-TRAIT ANXIETY INVENTORY SCORES MEAN (±SE) FOR BOTH MEDITATION AND REST GROUPS, BEFORE AND AFTER THE EYES-CLOSED EXPERIMENTAL PERIOD

	State	p*	Trait	p*
Pre-experimental (meditation)	23.17 (2.84)	$p<0.01$	25.32 (2.29)	$p<0.05$
Pre-experimental (rest)	34.61 (4.98)		36.24 (7.56)	
Post-experimental (meditation)	22.05 (1.81)	$p<0.01$	24.19 (2.86)	$p<0.05$
Post-experimental (rest)	32.10 (4.69)		34.38 (7.31)	

*Scores were compared using the t-test for independent groups.

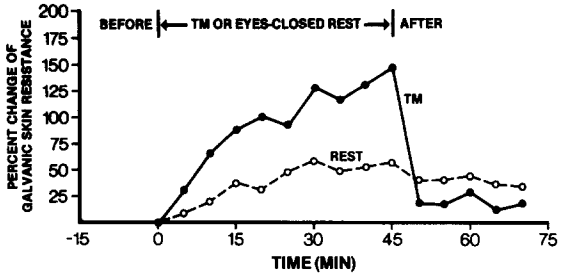

FIG. 2. Mean GSP values during and following the eyes-closed period for the TM group (●—●) and for the ordinary rest group (○— —○).

edly during TM (28%) with smaller decline accompanying rest (11%); these data have been reported previously [18].

EEG recordings showed no significant difference between the two groups, with alpha activity predominating during 90% of the eyes-closed period for both meditation and rest groups. Approximately 10% of the time was spent in stage I sleep.

DISCUSSION

The observed pAVP values in the meditation group are unusually high for healthy subjects. This elevation is not the result of a known endogenous rhythm, because AVP does not exhibit circadian variation during light hours in mammalian species, including man [27], although small, random nocturnal fluctuations of AVP averaging 0.6 μU/ml have been reported [13, 15, 29].

That elevation of pAVP in the meditation group is transient is indicated by the normal levels of AVP found in samples taken at a different time of day in each meditation subject. Also, if the increase in AVP levels had been sustained over a period of several hours prior to the experiment, plasma osmolality values would have been expected to be lower than those observed (due to antidiuresis). Finally, subjects did not exhibit obvious signs of excess water retention. Therefore, it seems probable that the elevation of AVP in these subjects is associated with their routine meditation practice at this time of day, although there was not an acute release of AVP precisely linked with meditation onset.

The high levels of AVP prior to the actual start of meditation practice (−15 min sample) suggests a process of conditioning. Such an effect has not, however, previously been reported in other studies of hormones in meditation. This may indicate that the physiologic processes associated with regular, daily elicitation of this behavior may induce and entrain vasopressin secretion. It is interesting that the putative conditioning process does not reflect in basal GSR, as well. However, the usual relationship between sympathetic activity and AVP secretion apparently does not apply in this behavior, as we discuss below.

The mechanism of increased AVP may be either decreased AVP clearance or increased AVP secretion from the posterior pituitary. The first alternative is unlikely for several reasons. AVP is primarily cleared by the liver and kidneys, and previous study [19] of the distribution of blood flow during meditation and rest found no difference of hepatic/renal blood flow between meditation and rest prior to the eyes-closed meditation/rest period. Although a 40% decline of hepatic blood flow during meditation was reported (with a 12% non-significant decline during rest), this decline would be expected to increase AVP values acutely by a maximum of 70% during or after meditation, assuming an 18 min half-life for AVP in whole blood and a secretion rate averaging 2000 μU/15 minutes [26]. This contrasts with the persisting concentrations of 2.6–7.1 times normal levels that were observed. It is therefore probable that the mechanism of increased AVP secretion is primary in the genesis of high plasma AVP concentration in the TM group rather than the mechanism of decreased clearance.

One of the most potent known stimuli of AVP release is blood hypertonicity. However, plasma osmolality values were normal for both groups at all points in the sampling series and did not change or differ significantly between groups. Additional, nonosmotic factors known to strongly potentiate AVP release in man include acute decline of arterial blood pressure, decrease in total blood volume, change in body posture and psychologic stress [26]. Increased AVP release due to acute drop in arterial blood pressure can be excluded because several studies have shown that meditation practice is not associated with acute variation of blood pressure [21,35]. Experimental procedures eliminated significant alteration of total blood volume or body posture as possible contributors to increased AVP secretion, since the small volumes of blood drawn during sampling were simultaneously replaced with identical volumes of isotonic saline, and subjects sat erect throughout the sampling period.

Several measures obtained in this study also rule out contribution of psychologic stress: GSR data indicated progressive decrease of sympathetic nervous system activity during the eyes-closed period for both groups; EEG activity recorded was consistent with relaxed wakefulness; marked decline of forearm muscle respiration in the meditation group indicated muscular relaxation [18]. Finally, before and after the experiment, STAI scores for the meditation group were significantly lower than those of the rest group and were well below average values for normal college age subjects [33] for both state anxiety (suggesting a decreased level of tension and apprehension) and trait anxiety (suggesting a decreased "anxiety proneness" or lessened tendency to respond to situations perceived as threatening with elevations in state anxiety intensity).

The high level of pAVP associated with meditation is, therefore, due to other than usually accepted homeostatic modulation of the releasing mechanism. It is of particular

interest that this state of decreased activation along with its opposite, states of stress, should both be associated with increased AVP secretion. The data of this study do not enable understanding of the specific mechanism of increased secretion. It is known, however, that either a special feature of TM and/or its repeated elicitation is associated with other hormonal changes, especially in the long-term practitioner, including increased prolactin [20] and markedly decreased cortisol secretion [17]. A role of subject selection is possible, although it is unlikely, since pAVP levels of the magnitudes have not been observed in a large number of [26] measurements this laboratory except in cases of disease

If the increased AVP secretion in this study is not associated with either homeostasis or stress, it seems reasonable to propose an action related to the behavioral effects of meditation practice. Such an action presumes an ability of peripheral AVP to affect the central nervous system. This would not be incongruent with previous reports [4–8] which have shown an ability of peripherally-administered AVP (as well as synthetic AVP analogs) to affect learning and memory. The mechanism of action in such instances is not clear. In particular, the question of blood-brain barrier (BBB) penetration has yet to be answered, although it is widely held that neuropeptides in general do not cross the BBB in biologically significant amounts. It should be noted, however, that retrograde transport of pituitary hormones back into the brain may provide an explanation [7]

Based upon evidence this ability of peripherally-administered AVP and its analogs to modify human and animal behavior, it is tempting to speculate that increased peripheral AVP activity may mediate reported effects of TM on learning, memory, and psychotherapeutic processes [11, 12, 32], and that the mechanism of its increased secretion in meditation may be more specifically related to its role as a psychochemical. Their data also further support previous research indicating specificity of TM (in the very long-term subject) among rest states in its effects on hormones, metabolism, and circulation [17–20]

ACKNOWLEDGEMENTS

The authors wish to acknowledge gratefully the financial support of The National Institute of Health, Grant No NHLBI27894 and the MacArthur Foundation in this research

NOTE ADDED IN PROOF

In measurements just completed, plasma oxytocin concentrations have been found to be normal and unchanged during the experiment in both meditation and rest subjects.

REFERENCES

1. Beckwith, B. F , T Petros, S. Kanaan-Beckwith, D. E. Cook, R J. Haug and C. Ryan Vasopressin analogy (DDAVP) facilitates concept learning in human males *Peptides* **3:** 627–630, 1982.
2. Bujatti, M. and P Riedere. Serotonin, noradrenaline, dopamine metabolites in transcendental meditation technique *J Neural Transm* **39:** 257–267, 1976
3. Davidson, R J., D. J. Goleman and G E Schwartz. Attentional and affective concomitants of meditation· a cross-sectional study. *J Abnorm Psychol* **85:** 235–238, 1976.
4. de Weid, D. and W. H. Gispen. Behavioral effects of peptides. In: *Peptides in Neurobiology*, edited by H. Gainer New York: Plenum, 1980, pp 397–448
5. de Weid, D. Behavioral effects of intraventricularly administered vasopressin and vasopressin fragments *Life Sci* **19:** 1147–1153, 1976
6 de Weid, D. and B. Bohus Modulation of memory processes by neuropeptides of hypothalamic-neurohypophyseal origin. In· *Brain Mechanisms in Memory and Learning*, edited by M A. Brazier. New York: Raven Press, 1979, pp 139–149
7 de Weid, D., J. J. Legros, P. Gilot, X. Seron, J. Claesseus, A. Adams, J M. Moeglen, A Audibert and P Perchier. Influence of vasopressin on learning and memory. *Lancet* **1:** 41, 1978
8. de Weid, D The role of the posterior pituitary and its peptides on the maintenance of conditioned avoidance behavior. In *Hormones and Brain Function*, edited by K. Lissak. New York· Plenum, 1973, pp. 391–398
9 Ehrensing, R H., G. F Miichell and R P. Baker. Vasopressin's effects on acquisition and extinction of conditioned avoidance response to smoking. *Peptides* **3:** 527–535, 1978
10 Ferguson, P. and J Gowan. TM—some preliminary psychological findings. *J Hum Psychol* **16:** 51–57, 1976.
11 Frumkin, L R. and R. R Pagano. The effect of Transcendental Meditation on right hemisphere functioning *Biofeedback Self-regulation.* **4:** 313–319, 1979
12 Glueck, B C. and C F Stroebel. Biofeedback and meditation in the treatment of psychiatric illness *Comp Psychiatry* **16:** 303–321, 1975
13 George, C. P. L., F. H. Messerli, J Genest, W. Nowaczynski, R Boucher, O. Kuchel and M Rojo-Ortega Diurnal variation of plasma vasopressin in man *J Clin Endocrinol Metab* **41:** 332–338, 1975.
14. Glass, G. V., V L. Willson and J M. Gottman. *Design and Analysis of Time Series Experiments.* Boulder· University of Colorado Press, 1975.
15 Gold, P W., F. K. Goodwin, J. C. Ballenger, H Weingartner, G. L. Robertson and R. M. Post Central vasopressin function in affective illness In: *Hormones and the Brain*, edited by D deWeid and P. A van Keep. Baltimore: University Park, 1978, pp. 241–254.
16. Hjelle, L. A. Transcendental meditation and psychological health *Percept Mot Skills* **39:** 623–624, 1974.
17 Jevning, R A., A. F. Wilson and J. M Davidson. Adrenocortical activity during meditation. *Horm Behav* **10:** 54–59, 1978.
18 Jevning, R A , A. F. Wilson and J. P O'Halloran Forearm blood flow and metabolism during stylized and unstylized states of decreased activation. *Am J Physiol* **245:** R110–R116, 1983
19. Jevning, R A , A. F. Wilson, W P Smith and M. E. Morton Redistribution of blood flow in acute hypometabolic behavior *Regul Integr Comp Physiol* **4:** R89–R92, 1978.
20. Jevning, R. A , A. F. Wilson and E. F. Vanderlaan. Plasma prolactin and growth hormone during meditation. *Psychosom Med* **40:** 329–333, 1978.
21 Michaels, R. R., J. Parra, D S McCann and A. J Vander Renin, cortisol and aldosterone during transcendental meditation *Psychosom Med* **41:** 50–54, 1979.
22. Nidich, S , W. Seeman and T. Dreskin. Influence of transcendental meditation: a replication. *J Couns Psychol* **22:** 565–566, 1973.
23. Pelletier, K. R. Influence of transcendental meditation upon autokinetic perception. *Percept Mot Skills* **39:** 1031–1034, 1974
24. Rechstaffen, A. and K. Kales. *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects.* Los Angeles, CA: Brain Information Service/Brain Research Institute, 1968. (UCLA Natl. Inst. Health Publ 204).

25. Reppert, S M., H. G. Artman, S. Swaminathan and D. A. Fisher. Vasopressin exhibits a rhythmic daily pattern in cerebrospinal fluid but not in blood *Science* **213:** 1256–1257, 1981.
26 Robertson, G. L. Vasopressin function in health and disease. *Recent Prog Horm Res* **33:** 333–385, 1977.
27. Rubin, R. T., R. E. Poland, P. R. Govin and B. B. Tower. Secretion of hormones influencing water and electrolyte balance (antidiuretic hormone, aldosterone, prolactin) during sleep in normal adult men. *Psychosom Med* **40:** 44–49, 1978.
28. Seeman, W., S. Nidich and T. Banta. Influence of transcendental meditation on a measure of self-actualization. *J Couns Psychol* **19:** 184–187, 1972.
29. Schwartz, W. J., R. J Coleman and S. M Reppert. A daily vasopressin rhythm in rat cerebrospinal fluid. *Brain Res* **263:** 105–112, 1983.
30. Shapiro, A. P., G. E. Schwartz, D. C. Ferguson, D. D. Redman and S M. Weiss. Behavioral methods in the treatment of hypertension: A review of their clinical status. *Ann Intern Med* **86:** 626–636, 1977.
31. Skowsky, W. R , A. A. Rosenbloom and D. A. Fischer. Radioimmunoassay measurement of arginine vasopressin in serum: development and application. *J Clin Endocrinol Metab* **38:** 278–281, 1974
32. Smith, J. C. Psychotherapeutic effects of transcendental meditation with controls for expectation of relief and daily sitting. *J Consult Clin Psychol* **44:** 630–636, 1976.
33. Spielberger, C. D., R. L. Gorsuch and R. E Luschene. *State-Trait Anxiety Inventory* Palo Alto, CA: Consulting Psychologists Press, 1968.
34. Vranckx, C., P Minne, A Beghezal, J M. Moeglen and A. Audibert Vasopressin and schizophrenia. In. *Biological Psychiatry Today,* edited by J. Obiols *et al* New York. Elsevier, 1979, pp. 753–758.
35. Wallace, R. K., H. Benson and A. F. Wilson. A wakeful hypometabolic physiologic state. *Am J Physiol* **221:** 795–799, 1971