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The low glutamate diet reduces blood pressure in veterans with Gulf War Illness

A CONSORT randomized clinical trial

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Abstract

Background: Gulf War Illness is a multi-symptom condition affecting veterans of the 1990 to 1991 Gulf War, which often presents with comorbid hypertension. The purpose of this study was to analyze the effects of the low glutamate diet, as well as an acute challenge of monosodium glutamate (MSG)/placebo, on resting heart rate, blood oxygenation level, and blood pressure (BP) in this population.

Methods: These data were measured at 4 time points: baseline, after 1 month on the low glutamate diet, and during each challenge week, where subjects were randomized into a double-blind, placebo-controlled, crossover challenge with MSG/placebo over 3 days each week. Pre-post diet changes were analyzed using paired *t* tests, change in the percentage of veterans meeting the criteria for hypertension was compared using chi-square or Fisher exact tests, and crossover challenge results were analyzed using general linear modeling in SAS® 9.4.

Results: There was a significant reduction in systolic BP (sitting and recumbent; both $P < .001$) and diastolic BP (sitting; $P = .02$) after 1 month on the diet. The percentage meeting the criteria for hypertension was also significantly reduced ($P < .05$). Challenge with MSG/placebo did not demonstrate an acute effect of glutamate on blood pressure.

Conclusion: Overall, these findings suggest that the low glutamate diet may be an effective treatment for lowering blood pressure in veterans with Gulf War Illness. This dietary effect does not appear to be driven by reduced consumption of free glutamate, but rather, by an increase in consumption of non-processed foods.

Abbreviations: BP = blood pressure, DASH = Dietary Approaches to Stop Hypertension, DBP = diastolic blood pressure, MSG = monosodium glutamate, SBP = systolic blood pressure, SD = standard deviation, SpO_2 = blood oxygenation level.

Keywords: blood pressure, diet, glutamate, Gulf War Illness, heart rate

1. Introduction

Gulf War Illness is a multi-symptom condition which includes widespread pain, fatigue, cognitive difficulties, sleep disturbances, gastrointestinal issues, anxiety, and depression. These symptoms have been reported by veterans of the 1990 to 1991 Gulf War, which was a US-led response to the invasion and annexation of Kuwait by Iraq.[1] Shortly after the end of the war, service men and women began experiencing the aforementioned symptoms.[2] Hypertension, or high blood pressure, was one of the top 5 most recorded afflictions in this population, even though it is not typically included in the definition of Gulf War Illness, with 35.3% of women and 43.6% of men being affected.[3] This is greater than the rate of hypertension in the general population of the same age group (age 40–59), where 29.4% of women and 37.2% of men report a diagnosis of hypertension.[4]

In 2017, the American College of Cardiology and American Heart Association lowered the cutoff for hypertension to be defined as a systolic blood pressure (SBP) measurement of ≥130 mm Hg or a diastolic blood pressure (DBP) measurement of ≥80 mm Hg.[5] More recently, the International Society for Hypertension released their 2020 guidelines which are in alignment with the previous US criteria with hypertension defined as a SBP of ≥140 mm Hg or a DBP of ≥90 mm Hg.[6] The causes of hypertension vary, but are commonly related to kidney disease,

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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obesity, and alcoholism, of which, obesity and alcoholism have been observed in veterans of the Gulf War.[7–12] Long term hypertension can lead to health complications and increased risks for stroke, heart disease, and subsequent complications.[13,14] Those at a higher risk for hypertension include men below the age of 60 when compared to their female counterparts, and vice versa at ages >60.[3,15] Furthermore, Black individuals are more prone to hypertension when compared to white individuals, and risk also tends to increase with age.[4,16]

Studies have suggested that glutamate, the major excitatory neurotransmitter in the central nervous system, may be able to influence blood pressure. One animal study found that after an 8-week exercise protocol, renovascular hypertensive rats experienced reduced levels of both mean arterial pressure and glutamate in the paraventricular nucleus of the hypothalamus, illustrating a possible positive correlation between glutamate and blood pressure.[17] In the same study, the renovascular hypertensive rats were microinjected with a glutamate receptor antagonist and hypertension was observed to decrease for that experimental group; suggesting that glutamate may be able to affect hypertension.[17] Similarly, another animal study also demonstrated that suppression of glutamate binding may reduce hypertension.[18] Additionally, chronic intake of monosodium glutamate (MSG) has been associated with increased SBP and DBP in human subjects.[19] This study collected food frequency questionnaires and blood pressure measurements of individuals and households in rural and urban China over the course of 5 years.[19] However, it should be noted that there is also evidence for the opposite effect, where glutamate stimulation of the N-methyl-D-aspartate receptor has been associated with vasodilation (mediated by nitric oxide release), which should theoretically cause a decrease in blood pressure.[20]

There is currently no published literature studying the effects of the low glutamate diet on blood pressure. Hence, the objective of this analysis was to examine the effects of the low glutamate diet, as well as acute challenge with MSG versus placebo, on the blood pressure of veterans with Gulf War Illness.

2. Methods

The study was registered at ClinicalTrials.gov (NCT#03342482) and was approved by the Institutional Review Board. All subjects provided written informed consent before participating.

2.1. Data collection methods

The research coordinator recruited forty veterans with Gulf War Illness from across the US from October 2017 through January 2020, with follow-up occurring over the 3 months following the end of each subject's formal participation in the study. Sample size was determined based on other primary endpoints included in the clinical trial (like overall symptom number). No sample size calculation was computed based on blood pressure change. This is the first time that the association between the low glutamate diet and BP has been tested; thus, there was no mean (standard deviation [SD]) change data available for this computation. Thus, the preliminary findings presented herein can be used for sample size calculations for future research. The trail ended once the recruitment goals were met. The methods of this study (and CONSORT diagram) have been published previously; however, the methods related to the pertinent measurements are quickly summarized here.[10] To assess eligibility, all veterans were screened to make sure that they fulfill both the Kansas City and Centers for Disease Control and Prevention criteria for Gulf War Illness.[21,22] They also had to be <75 years of age, on a stable medication regimen for 3 months or more (and willing to keep the type, dosage, and frequency of medications stable throughout the study), and also willing to change their diet and discontinue use of alcohol and cannabis during the study. Potential subjects were excluded if they had a substance use disorder in the past year, if they currently smoked, if they had a seizure disorder or severe asthma, or if they were taking any medications which affect glutamatergic neurotransmission. Subjects traveled to Washington, DC 2 times, first to obtain baseline measurements (pre-diet values), and then again after 1 month on the low glutamate diet. Training on the low glutamate diet was done via Skype on a Thursday or Friday; preparation to start the diet occurred over the weekend, and subjects started the diet the following Monday. All subjects received training materials, including a list of food additives to avoid, shopping instructions, a list of foods highest in each micronutrient, a list of foods highest in antioxidants, and sample recipes. Dietary compliance was measured using a specially designed glutamate food frequency questionnaire which asked about consumption of foods which typically contain free glutamate (i.e. glutamate not bound to a protein). After 1 month on the diet, participants returned to the lab for post-diet assessments, and then using computer generated randomization produced by the principal investigator, subjects were placed into a 2-week challenge period where they orally received either 5 g of MSG or 5 g of a sugar/salt mixture in vegetable capsules. The sodium content of the placebo was matched to that of the MSG. The subjects received pills in the morning, over 3 consecutive days, after an overnight fast. After a 1-week wash-out period, subjects came into the lab again in the morning for 3 consecutive days to receive the opposite contingency. The challenge week randomization schedule was given to the un-blinded research assistant who created the MSG and placebo vegetable capsules. This individual had no interaction with the participants.

Blood pressure was measured in 2 ways at the pre-diet and post-diet visits. First, blood pressure was measured with a digital sphygmomanometer while the participant was in a sitting position without speaking. At this same time, blood oxygenation levels (SpO_2) and heart rate were measured with a finger pulse oximeter. Then a second blood pressure measurement was taken after the participant had been lying in a recumbent position with their eyes closed for 3 minutes without speaking or moving.

During the 2 randomized double-blind placebo controlled crossover challenge weeks, repeated blood pressure, pulse, and SpO_2 measures were taken over the 3 days each week during the 2-hour observation period (at the 1-hour and 2-hour mark) after the pills with MSG or placebo were consumed. The pills were kept in numbered containers to ensure the blind was maintained from both subjects and study staff. Averages were compared across weeks, and across first and second measurements, to look for timing effects. Additionally, blood pressure and pulse were recorded in a recumbent position, similar to the pre-diet and post-diet measurements, after 3 minutes of lying down with their eyes closed and without moving or speaking.

2.2. Statistical methods

All data were double entered into Microsoft® Excel® and cross-checked for accuracy. All analyses were completed with the use of SAS® 9.4. The difference between pre-diet and post-diet values for quantitative variables was assessed with paired *t* tests. New variables for hypertension with stages 0, 1, and 2 were coded using the 2017 and 2020 guidelines, as described here. Based on the 2017 guidelines, if the average SBP was ≥140 or average DBP was ≥90 mm Hg, then this would be considered stage 2 hypertension, with stage 1 hypertension being considered an SBP of 130 to 140 mm Hg or a DBP measurement between 80 and 90 mm Hg.[6] For the 2020 guidelines, stage 2 hypertension was defined as an average SBP ≥160 or average DBP ≥100 mm Hg, and stage 1 hypertension was considered 140 ≤ average SBP < 160 or 90 ≤ average DBP < 100 mm Hg.[7] Additional Yes/No categorical hypertension variables

were coded, with those in stage 1 or 2 being labeled as having hypertension. A chi-square test (or Fisher exact where appropriate) was used to compare the proportion of subjects with hypertension pre-diet as compared to post-diet, as well as to compare changes in hypertension stage. Average blood pressure, SpO_2, and pulse measurements were compared between challenge weeks of the crossover design with differentiation of measurement time point and position using a paired *t* test. The significance level $a = 0.05$ was used for all analyses.

3. Results

The participants in this study had a mean (SD) age of 54 (6) years. Of the forty participants, 27.5% were female and 72.5% were male with 92.5% of them being Caucasian and 7.5% being Black. Half of the participants had served in the Army, 15% in the Air Force, 13% in the Navy, and 20% in the Marine Corps. No medication changes were reported throughout the study period.

The mean (SD) measurements of SBP, DBP, pulse, and SpO2 for each time period within the study were compared using paired *t* tests. SpO2 was not taken in the recumbent position, so this data is not included. Significant improvements in SBP were observed for both sitting and recumbent measurements after one month on the low glutamate diet, whereas a significant decrease in DBP was only observed for the sitting measurement. Resting heart rate measurements also significantly improved in both positions. There were no significant changes in the participants' SpO2 before and after the diet (Table 1).

Based on the 2017 American College of Cardiology/American Heart Association criteria for hypertension, 58% (23/40) of the participants were hypertensive at baseline, but after 1 month on the low glutamate diet, only 48% (19/40) met the criteria for hypertension ($P = .05$, chi-square).[5] Significant improvements were also noted by hypertension stage ($P = .03$, chi-square) (Fig. 1A). When using the 2020 International Society of Hypertension criteria, 22.5% (9/40) participants were defined as hypertensive at baseline, and this was reduced to 15% (6/40) after 1 month on the diet ($P = .02$, chi-square) (Fig. 1B).[6]

During the challenge period, there were no significant differences identified using generalized linear modeling for measurements of SBP, DBP, SpO_2 (sitting position only), or resting heart rate between the MSG or placebo groups in either their seated or recumbent measure(s) obtained on the final day of the challenge week treatment administration (Table 2).

Average measurements were also compared during each challenge week using paired *t* tests, comparing the average measurements after 1 hour and after 2 hours, to examine whether acute timing effects of MSG may be present. No differences were noted between these 2 time points for the MSG week, however, differences were observed during the placebo week, where subjects received capsules containing sucrose plus salt (with the amount of sodium being matched to the MSG week). There was a significant increase in both SBP and DBP 2 hours after receiving the placebo pills (Table 3).

The SBP and DBP values measured at the 2 time points on each day of both challenge weeks were averaged based on challenge sequence, for those receiving placebo then MSG, versus those receiving MSG and then placebo, and these averages were compared using paired *t* tests. Slight variations in response were seen when comparing the order in which subjects received the challenge materials (Figs. 2A and B); however, overall, no significant acute effects of MSG on blood pressure were observed.

4. Discussion

After 1 month on the low glutamate diet, there was a significant reduction in SBP, DBP, resting heart rate, and the percentage of subjects meeting the criteria for hypertension. However, upon challenge with MSG, as compared to placebo, no significant increase in these measures was observed, suggesting that other aspects of the diet are responsible for this beneficial effect on the cardiovascular system.

The low glutamate diet is a healthy whole food diet which restricts consumption of free glutamate found in food additives and some naturally occurring food sources, while concurrently optimizing intake of foods naturally high in micronutrients and antioxidants. It is comparable to the Dietary Approaches to Stop Hypertension (DASH) diet in that it promotes consumption of fruits, vegetables, and dairy, but differs from the DASH diet in that there is no restriction on sodium consumption. The DASH diet has been shown to lower SBP by an average of 8.90 mm Hg and DBP by an average of 4.50 mm Hg in a seated position after 1 month on the diet.[23] The low glutamate diet reduced SBP by an average of 11.6 mm Hg sitting, and DBP by an average of 4.9 mm Hg sitting, and thus, was similar to, or slightly better than, the DASH diet over the same duration of time.

A reduction in resting heart rate was also observed in this study after 1 month on the low glutamate diet. A lower resting heart rate has been associated with better health outcomes. One study found that men and women (mean age of 55.3 years) with a resting heart rate <60 bpm were at a significantly lower risk of mortality for lung, breast, colorectal, and kidney cancers, as well as cardiovascular disease, when compared to those with a resting heart rate >80 bpm.[24] Physical activity also has the ability to positively affect resting heart rate.[25] Many other factors such as genetics, overall physical well-being, and diet are understudied in regards to resting heart rate.[26] To our knowledge, no studies have been conducted to evaluate the effects of diet

Table 1

Comparison of average SBP, DBP, SpO_2†, and resting heart rate values, taken in a sitting position and in a recumbent position, at pre-diet and after 1 month on the low glutamate diet using a paired *t* test.

N = 40	Sitting – prior to blood draw			Recumbent for 3 min		
	Pre-diet	Post-diet	*P* value	Pre-diet	Post-diet	*P* value
	Mean (SD)			Mean (SD)		
SBP (mm Hg)*	144.00 (18.71)	132.40 (15.52)	.0005*	130.38 (14.11)	124.50 (12.14)	.007*
DBP (mm Hg)†	88.75 (11.38)	83.88 (10.71)	.02*	76.00 (8.79)	74.65 (9.98)	.26
SpO_2 (%)‡‖	96.60 (2.62)	97.35 (1.35)	.07	–	–	–
Pulse (bpm)§	74.60 (12.07)	71.40 (11.20)	.04*	68.50 (8.97)	66.12 (7.89)	.05*

DBP = diastolic blood pressure, SBP = systolic blood pressure, SD = standard deviation, SpO_2 = blood oxygenation level.

*Systolic blood pressure in mm Hg.

†Diastolic blood pressure in mm HgSpO_2 was not obtained in the recumbent position.

‡Percentage of blood oxygenation.

§Beats per minute.

‖SpO_2 was not obtained in the recumbent position.

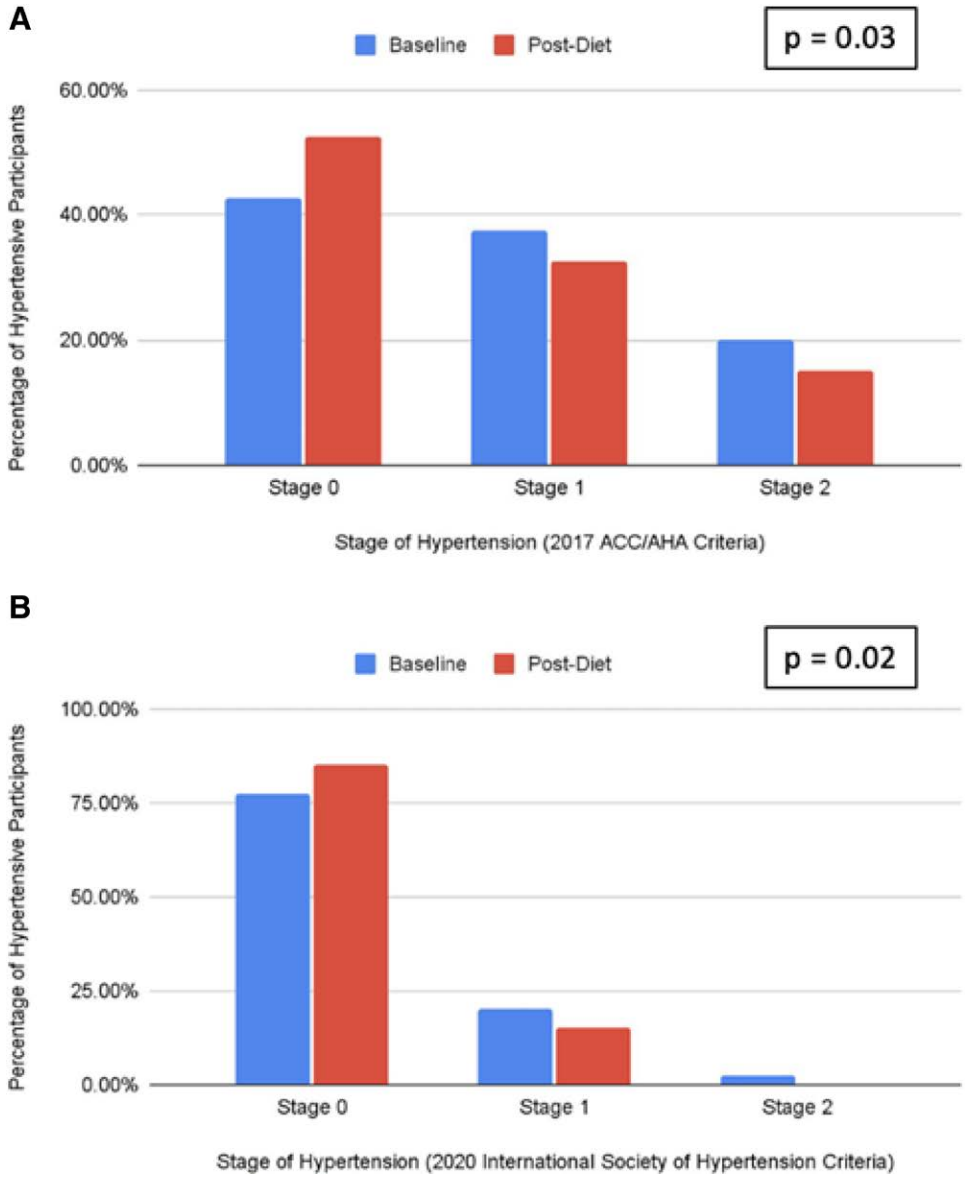

Figure 1. Baseline versus post-diet comparison of the percentage of hypertensive participants at each time point using a chi-square test. The comparison of the percentage of participants at each stage of hypertension at baseline and post-diet was obtained using (A) the 2017 ACC/AHA criteria for hypertension 5 and (B) the 2020 International Society of Hypertension criteria for hypertension 6. ACC = American College of Cardiology, AHA = American Heart Association.

Table 2

Comparison of the effects of the acute challenge of MSG versus placebo on average measures of SBP, DBP, SpO_2, and pulse taken while sitting on days 1 to 3 of each challenge week and on recumbent measurements taken on the third day of each challenge week using a paired *t* test.

N = 39	Average of sitting measurements taken on days 1–3 of each challenge wk			Recumbent measure on day 3 of each challenge wk		
	Placebo	MSG	*P* value	Placebo	MSG	*P* value
	Mean (SD)			Mean (SD)		
SBP (mm Hg)*	127.56 (10.45)	127.81 (14.58)	.87	123.10 (12.70)	122.56 (9.97)	.75
DBP (mm Hg)†	80.57 (8.76)	79.38 (10.98)	.20	72.92 (10.16)	71.62 (10.15)	.27
SpO_2 (%)‡‖	96.61 (1.03)	96.82 (1.12)	.11	–	–	–
Pulse (bpm)§	68.86 (10.10)	68.61 (8.92)	.80	69.18 (9.71)	69.86 (9.66)	.58

DBP = diastolic blood pressure, MSG = monosodium glutamate, SBP = systolic blood pressure, SD = standard deviation.
*Systolic blood pressure in mm Hg.
†Diastolic blood pressure in mm HgSpO_2 was not obtained in the recumbent position.
‡Percentage of blood oxygenation.
§Beats per minute.
‖SpO_2 was not obtained in the recumbent position.

Table 3

Comparison of time point differences in average measurements at hour 1 and hour 2 of the monitoring period across 3 days for measurements during each challenge week using a paired *t* test.

	Placebo wk			MSG wk		
N = 38	Avg h 1	Avg h 2	*P* value	Avg h 1	Avg h 2	*P* value
	Mean (SD)			Mean (SD)		
SBP (mm Hg)*	126.67 (10.66)	129.68 (9.87)	.003*	128.96 (13.86)	128.60 (13.57)	.68
DBP (mm Hg)†	80.19 (8.32)	81.83 (9.05)	.02*	80.30 (9.95)	79.87 (11.12)	.63
SpO_2 (%)‡‖	96.75 (1.06)	96.57 (1.16)	.26	96.87 (1.15)	96.85 (1.24)	.91
Pulse (bpm)§	69.11 (10.39)	68.14 (10.14)	.09	68.80 (8.51)	68.22 (10.16)	.49

DBP = diastolic blood pressure, MSG = monosodium glutamate, SBP = systolic blood pressure, SD = standard deviation, SpO_2 = blood oxygenation level.

*Systolic blood pressure in mm Hg.

†Diastolic blood pressure in mm Hg SpO_2 was not obtained in the recumbent position.

‡Percentage of blood oxygenation.

§Beats per minute.

‖SpO2 was not obtained in the recumbent position.

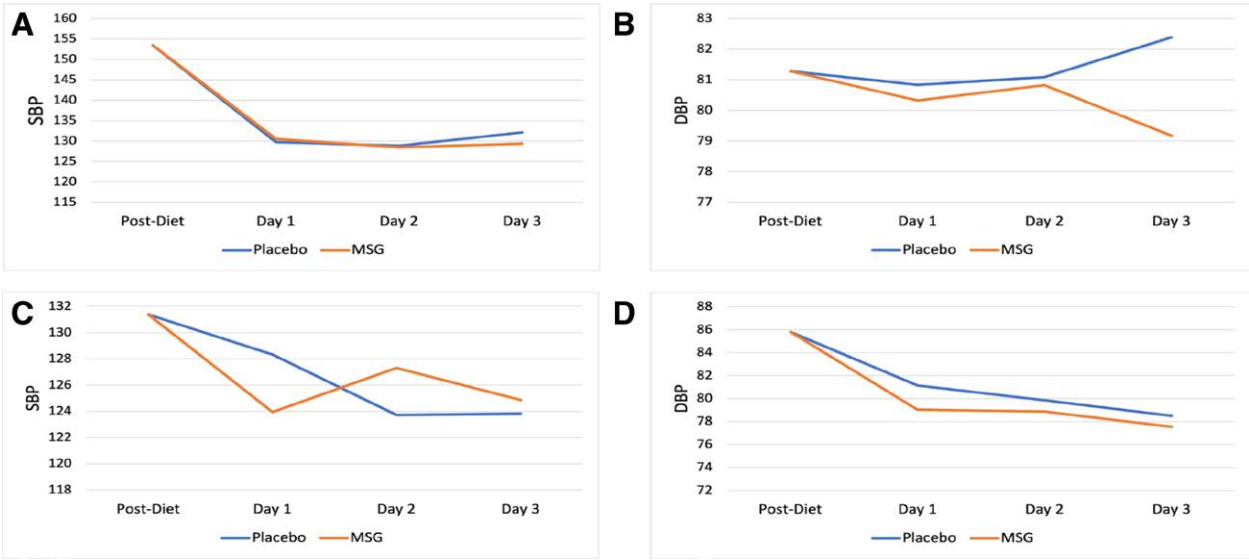

Figure 2. Average recumbent blood pressure measurements at post-diet and during the 3-day treatment period of each challenge week. (A) Average recumbent SBP measurements for the placebo then MSG group. (B) Average recumbent SBP measurements for the MSG then placebo group. (C) Average recumbent DBP measurements for the placebo then MSG group. (D) Average recumbent DBP measurements for the MSG then placebo group. DBP = diastolic blood pressure, MSG = monosodium glutamate, SBP = systolic blood pressure.

on resting heart rate. The low glutamate diet may have reduced resting heart rate through decreased excitatory stimulation of the heart via glutamate neurotransmission. The heart has glutamate receptors, and these have been implicated in heart physiology, excitation, and pathophysiology.[27] However, no acute effect of glutamate challenge on resting heart rate was observed in this study.

During the challenge weeks, subjects had their blood pressure taken in a seated position at 1 hour and 2 hours after pill consumption for all 3 days of each week. A comparison of the average SBP and DBP after 1 hour was compared to the 2-hour measure for each challenge material to test for acute reaction which may vary between time points (i.e., a timing effect). Interestingly, a timing effect was observed for SBP and DBP during the placebo week, but not for the MSG week. For the placebo week, the SBP and DBP were significantly higher after 2 hours than after 1 hour. Since the placebo and MSG pills were matched for sodium content, this suggests a potential acute effect of sucrose on increasing participants' blood pressure levels during the placebo challenge week. There is very limited literature on the acute impact of sucrose on blood pressure. One study found that a sugar water mixture with lemon juice led to a significant decrease in blood pressure in healthy, older participants, with a bigger effect after the 60-minute mark.[28] This evidence that sucrose may acutely decrease blood pressure conflicts with findings from this study. To our knowledge, there are no other published studies examining the acute effects of sucrose on blood pressure.

This study had multiple strengths including a study design which allowed for testing blood pressure in multiple positions and multiple time points, as well as the inclusion of a double-blind, placebo-controlled crossover challenge with MSG versus placebo to directly test for effects of glutamate on blood pressure (while consumption of dietary glutamate was controlled). The sodium content of the placebo condition was matched to the amount of sodium in MSG, thereby controlling for any effects of sodium in the acute challenge phase of the study.

However, this study is limited by the small sample size and lack of control BP measurement to assess changes in blood pressure over time in an untreated group, which excludes the ability to rule out any regression to the mean. This study also cannot address, or account for, the potential for long term intake of free glutamate to influence these measures in a negative manner. Since the low glutamate diet also emphasizes increased consumption of nutrients which are protective against excitotoxicity, it is also possible that improved nutrient intake may have been protective against acute BP response during the challenge period.

Dietary adherence was measured using a specially designed food frequency questionnaire listing the most commonly consumed foods high in glutamate, and change in this measure has previously been shown to correlate strongly with other improvements on the low glutamate diet; however, this self-reported measure may be less reliable than plasma measurement of glutamate levels. Future research will be needed to examine whether these results hold in a larger population of veterans with Gulf War Illness and to further examine the dietary mechanisms at play.

5. Conclusion

The results of this study suggest that the low glutamate diet may effectively reduce SBP, DBP, and resting heart rate in veterans with Gulf War Illness. No acute effects on blood pressure were observed during challenge with MSG in a double-blind, placebo-controlled, crossover design, which suggests that the diet's focus on healthy whole foods which are low in additives and high in micronutrients is more likely driving the observed effects on blood pressure. While consumption of healthy whole foods has been shown to reduce blood pressure in the DASH diet, this study shows that blood pressure may also be able to be reduced using the low glutamate diet, even without formally restricting salt consumption. Future research is needed to confirm these findings in a larger group of veterans with Gulf War Illness.

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