Original Article

TJPS

The Thai Journal of Pharmaceutical Sciences
38 (4), October-December 2014: 156-209

Acute effects of hot red chili on autonomic and metabolic functions in healthy subjects

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Abstract

To investigate if chili consumption as a food ingredient in a fried rice meal would have any real acute pharmacological effects on autonomic nervous system (ANS) and metabolic system (MS), a randomized, cross-over, intervention trial was conducted in 33 healthy subjects. The study found that a moderate dose of chili (containing 16.96 - 24.40 mg capsaicin plus 4.86 - 6.99 mg dihydrocapsaicin) given in a meal significantly increased systolic blood pressure and decreased rMSSD (the square root of mean of sum of square of successive difference) parameter of heart rate variability reflecting a reduced parasympathetic function of the ANS. Chili also affected MS by significantly reducing the body temperature, but not other MS parameters. Time-passing also had highly significant effects on ANS and MS. However, the linear mixed modeling revealed that there was little evidence that chili modified the physiological response over a 180 min period. This result suggests that the body's strong physiologic responses modulate any chili effects to the extent that there are minimal differential responses over the experimental period. These findings confirmed that moderate amount of chili in food have significant acute effects on the modulation of ANS and MS but not therapeutic effect on weight reduction.

Keywords: Chili, Capsaicin, Autonomic nervous system, Metabolic system, Heart rate variability

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Received: 05 June 2014
Revised: 12 September 2014
Accepted:11 November 2014

Academic Editor: Nithipun Suksumek

Introduction

Several studies have shown various pharmacological effects of chili, in particular, effects on autonomic nervous system (ANS) and metabolic system (MS) in animals [1-6] and humans [7-9]. However, most of these studies' designs did not follow the natural practice of chili consumption in the Thai population. Since hot red chili is one of the vital ingredients in Thai food, it is questionable whether there would be any real health effects from this consumption. Therefore, we conducted experiments to investigate acute pharmacological effects on ANS and MS among healthy subjects.

Materials and Methods

The study was approved by Khon Kaen University's Ethics Committee on research in human subjects (HE522084). The study was a randomized, cross-over, and intervention trial.

Subjects: Thirty-three young healthy normal-weighted subjects (7 males, 26 females, mean age 21.2 ± 0.3 years, Body Mass Index 20.0 ± 0.2) without history of diabetes, cardiovascular, liver, renal, and gastrointestinal diseases were recruited. They were instructed to abstain from spicy food (e.g., containing chili, pepper, etc.), alcohol, caffeine, drug and cigarettes 72 hours prior to the experiments. Each subject was assigned to each experimental arm (control or chili) with a minimum of 7 day washout for each experiment. The chili (treatment) arm involved a standard meal containing the specified dose of chili powder, whereas the control arm involved the consumption of the same standard meal without chili powder. Besides, subjects were fasted overnight for at least 8 hours before the experiments. Then they were randomized to start the experiment with or without chili.

Meals: Fried rice 5 g/kg BW was strictly prepared for individual subject by standard recipe comprising 12% protein, 21 % fat and 67 % carbohydrate. Nutritional compositions were calculated according to Guidelines of the Bureau of Department of Health and Nutrition, Ministry of Public Health, Thailand [10]. Dried powdered chili was prepared from local fresh red chili (purchased from local market, *C. frutesens*). One gram of dried powdered chili was derived from 3.307 ± 0.13 g fresh red chili. The powdered chili contained 2.925 ± 0.12 mg capsaicin and 0.838 ± 0.047 mg dihydrocapsaicin (analyzed with HPLC-UV detector, at 280 nm, using standards capsaicin 98 % (Calbiochem), dihydrocapsaicin 99% (Wako) [11]). For the chili (treatment) experiment, powdered chili was added into fried rice with a calculated dose of 0.4 mg/kg BW capsaicin. Thus, a meal with chili for each subject contained between 16.96 - 24.40 mg capsaicin and 4.86 - 6.99 mg dihydrocapsaicin.

Experimental procedures: After arrival and having at least 20 minutes rest, subjects (one subject at a time) were seated in an upright position. Heart rate variability (HRV) was measured by an autoregressive power spectral analysis during 10 min of RR electrocardiographic interval acquisition (ADInstruments PowerLab B/30). They were prepared for electrode placement to measure RR interval via a lead II EKG (electrocardiogram). Parameters of MS and ANS, and 5 mL blood samples were collected to analyze for baseline data (T_0). The subjects then took a meal of fried rice to finish within 15 min, with 200 mL of drinking water. Another 200 mL glass of water was given throughout the experiment.

Readings of EKG were recorded at least 5 min. All parameters and blood samples were collected at a 30 min interval until 180 min (T_0 - T_{180}) with subjects remaining in a seated position. Analysis for blood samples was performed by chemical clinic laboratory, Srinagarind Hospital.

Statistical analyses: The Linear mixed (effect) model (LMM) analysis for a crossover experiment was conducted to test for the chili effects (treatment vs. control), time effects (6 of 30 min intervals starting at baseline and finishing at 180 min), sequence effects (effects of initial allocation to treatment and control), and the interaction of these effects. All analyses were done using the R statistical package [12], and the LMM analysis was carried out using the 1me4 R library [13].

Results

Baseline clinical characteristics of subjects are shown in Table 1. The LMM analysis revealed that chili had significant effects on some ANS parameters, e.g., systolic blood pressure (SBP) (Figure 1(B)), rMSSD (the square root of mean of sum of square of difference between adjacent RR intervals or successive difference) (Figure 1(D)), and on MS parameters, e.g., body temperature (Figure 2(H)).

For the ANS parameters (Figure 1), chili were found to significantly increase SBP where value was found significantly higher in the chili experiment than the control experiment (mean difference = 3.03, 95% CI: 0.18, 5.88, $p<0.05$). Chili also led to significant reduction in the rMSSD (mean difference = -9.50, 95% CI: -18.42; -0.59, $p<0.05$). For the MS parameters (Figure 2), chili significantly decreased body temperature (mean difference = -0.36, 95% CI: -0.53, -0.18, $p<0.05$). Other ANS (Figure 1) and MS (Figure 2) parameters measured were found insignificant.

From the LMM analysis, time was also found to have highly significant effects on several ANS and MS parameters, so that significant differences from the start of the experiment (baseline values) were found at many experimental intervals.

Significant effects on the ANS parameters (Figure 1) resulting from the time effects were increases in the heart rate (Log likelihood ratio for the global effects of time or LRT, χ^2 = 52.32, $p<0.001$) where higher value was found at 30-150 min and SBP (LRT, χ^2 = 24.64, $p<0.001$) where higher value was found at 60 min, decreased rMSSD

Table 1 Baseline clinical characteristics of subjects

	Subjects (n = 33)		Males (n = 7)		Females (n = 28)	
	mean	**S.E.M.**	**Mean**	**S.E.M.**	**mean**	**S.E.M.**
Age (years)	21.2	0.3	21.1	0.7	21.2	0.4
Body mass index (BMI, kg/m^2)	20.0	0.2	20.4	0.4	19.8	0.2
Systolic blood pressure (SBP, mm Hg)	103.9	1.4	107.9	3.2	102.8	1.3
Diastolic blood Pressure (DBP, mm Hg)	67.2	1.3	73.6	2.9	65.5	0.9
Pulse rate [PR, per min)	73.1	1.2	70.4	2.1	73.8	1.2

(LRT, χ^2 = 14.45, p<0.05) where lower value was found at 30-150 min, increased low frequency of normalized unit (LF, nu) (LRT, χ^2 = 15.62, p<0.05) where higher value was found at 30-180 min, decreased high frequency of normalized unit (HF, nu) (LRT, χ^2 = 17.39, p<0.01) where lower value was found at 30 and 90-180 min, and increased very low frequency (VLF, ms^2) (LRT, χ^2 = 17.66, p<0.01) where higher value was found at 180 min.

For the ventilatory response, the time effects significantly increased expired total ventilation (LRT, χ^2 = 55.81, p<0.001) where higher value was found at 90-180 min (Figure 1(M)).

Figure 2 summarize the effects of chili on the MS parameters. It was observed that the time effects were to increase blood sugar (LRT, χ^2 = 241.47, p<0.001) where higher value was found at 30-180 min, blood insulin (LRT, χ^2 = 156.19, p<0.001) where higher value was found at 30-180 min, carbohydrate oxidation (LRT, χ^2 = 30.186, p<0.001) where higher value was found at 180 min, oxygen consumption (LRT. χ^2 = 37.99, p<0.001) where higher value was found at 60-180 min, carbon dioxide production (LRT, χ^2 = 37.99, p<0.001) where higher value was found at 60-180 min, energy expenditure (LRT, χ^2 = 57.33, p<0.001) where higher value was found at 60-180 min, body temperature (LRT, χ^2 = 80.42, p<0.001) where higher value was found at 30-180 min, respiratory exchange ratio (LRT, χ^2 = 58.83, p<0.001) where higher value was found at 30-180 min, expired total ventilation (LRT, χ^2 = 55.81, p<0.001) where higher value was found at 90-180 min.

The LMM also revealed that there was no significant interaction between the treatment and time effects on the ANS or MS. This was a somewhat surprising result given the experimental design specifically included these terms to detect differences in the ANS and MS responses over time between the treatment (chili effect) groups.

The sequence effect was never identified as significant, suggesting that the allocation of ‘order’ of treatment had little effect. The sequence term, by design, was not included to test any particular research hypothesis, but to detect, and remove, any treatment order effect.

Discussion

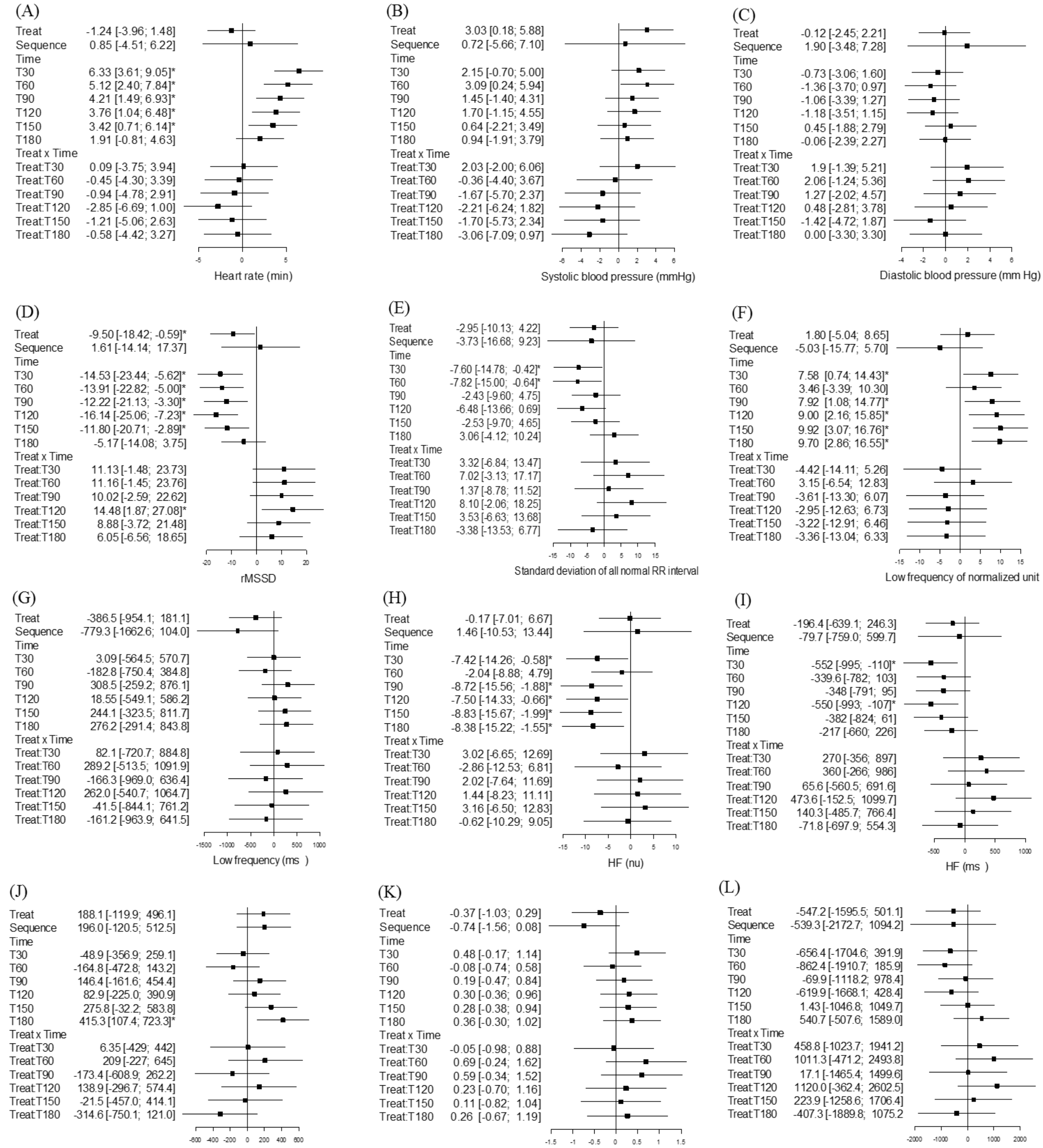
The heart rate variability or HRV represents one of the promising, noninvasive and reliable, markers to reflect ANS, with different parameters of HRV revealing specifically sympathetic or parasympathetic functions, i.e., total power and SDDN for the sum effects, HF and rMSSD for parasympathetic, LF for sympathetic, and LF/HF for sympathetic- parasympathetic balance[14-15]. In our study, we used 5-min HRV for each interval to detect the chili effects for the period of the 180 min experiment to identify whether there was/were alteration(s) in the ANS functions in addition to other ANS and MS parameters. Although many previous studies, both in experimental animals and humans, have demonstrated that chili increased sympathetic function [2-7], we clearly demonstrated differently in ANS functions. We found that chili significantly increased SBP and decreased the rMSSD. Therefore, our study suggests that chili significantly reduce parasympathetic nervous system. This finding is not consistent with previous studies [2-7]. This disagreement could be due to more parameters covered in our study. Although the two ANS functions (sympathetic and parasympathetic) are not independent in controlling the body’s physiologic system, our findings may demonstrate a more prominent tone of ANS affected by chili, i.e., parasympathetic system.

For the MS parameters, our study showed that chili significantly reduced the body temperature. This is in line with studies reported by Székely and Szolcsányi [16]and Lee, *et al.* [17]. Reports suggested that people residing in tropical climates preferred their food hotter than those in temperate climates and this pattern gave rise to the theory that eating hot, spicy food helps combat the warm climate via gustatory sweating [18]. Our finding supports this theory, although during consumption of chili the feeling of warmth or burning sensation may occur.

It was believed that people who eat plenty of hot and spicy food have a high metabolic rate and stay lean since several studies reported that chili or capsaicin enhanced energy expenditure and substrate oxidation [19-21] or reduced fat or carbohydrate uptake in later meals [7]. Animal experiments also showed that capsaicin enhanced oxygen uptake and reduced adiposity [1-3]. Thus, long term consumption would lead to weight reduction. Our acute study did not support this hypothesis since all MS parameters measured, i.e., blood sugar, blood insulin, carbohydrate oxidation, fat oxidation, oxygen consumption, carbon dioxide production, energy expenditure, respiratory exchange ratio, and expired total ventilation, with the exception of body temperature, did not show significant change in 180 min period.

There are substantial inconsistencies in the literatures regarding chili effects. Several studies demonstrate positive effects, while others show no, or even negative effects on the same parameters. This discrepancy may be due to differences in chili dosage and forms, experimental protocols and designs, or even the target populations under consideration. It is true that conditions in the studies may give the explanations for the differences. The metabolic control of the body is also unarguably complex since many systems determine the final outcome, e.g., ANS, endocrine system and environmental conditions. Giving human blood glucose and blood insulin as examples since they are typical parameters measured for testing metabolic effects of chili in many studies. While Chaiyasit, *et al.* [9] reported positive acute effects of chili in reducing glucose and stimulating secretion of insulin, Ahuja, et al [22] reported insignificance in these parameters in a 4-weeks-term study. In our finding, chili as a food ingredient have insignificant acute effects on blood glucose and blood insulin.

The weight reduction effects maybe the most attractive therapeutic effects of chili or capsaicin and it maybe of highest therapeutic impact on humans if confirmed as high proportion of human population are



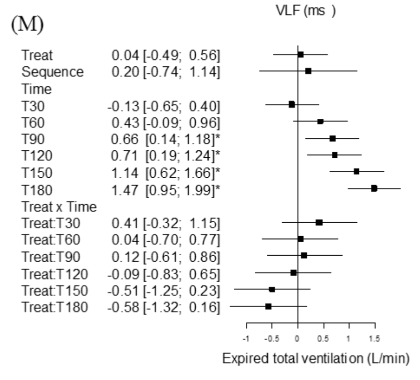
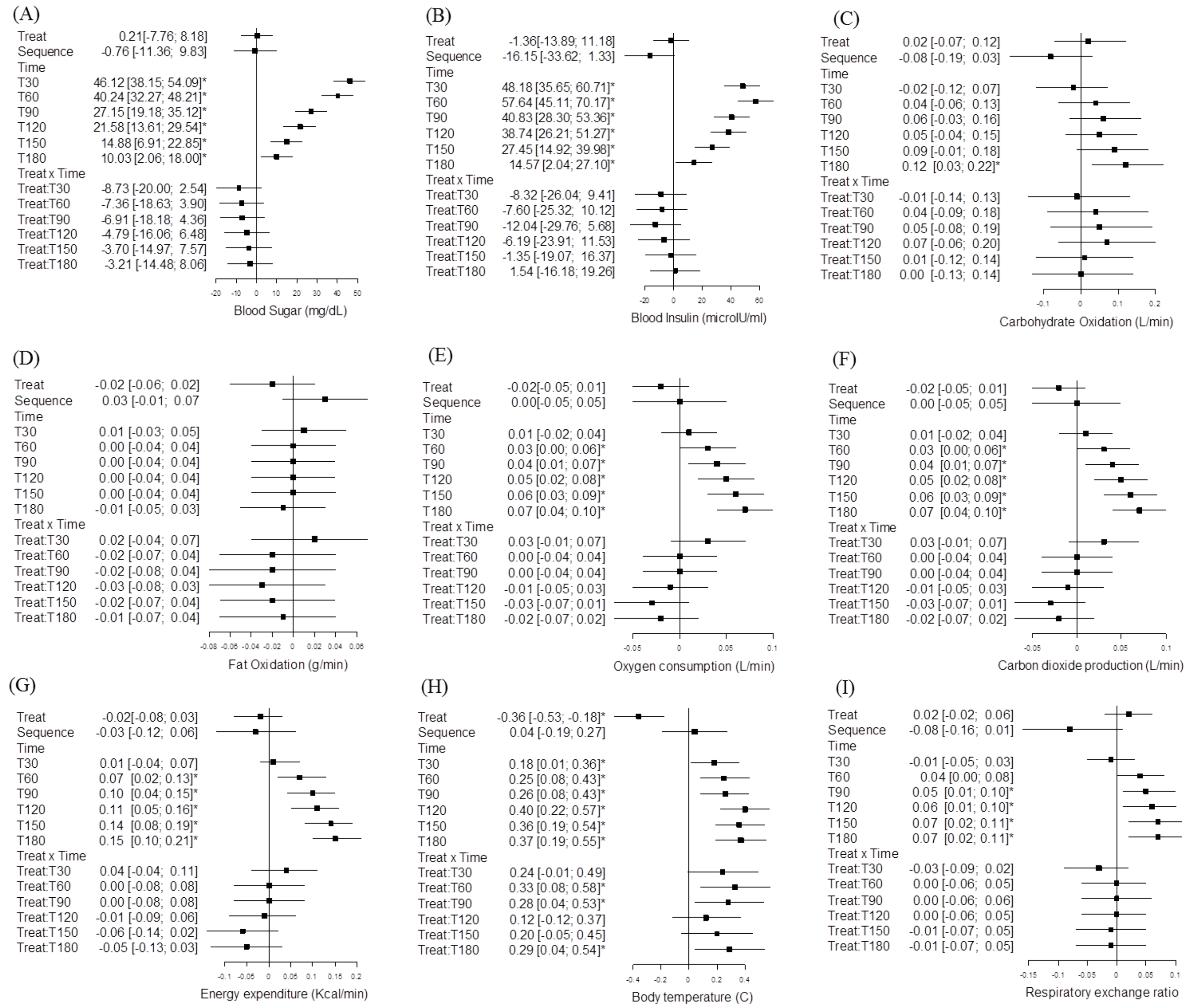


Figure 1 Graphical demonstrations (Forest Plot) of results from the linear mixed (effect) model (LMM) analysis for the chili effects (Treat), the sequence effects (initial allocation to treatment or control), the time effects (6 of 30 minute intervals, T30, T90,…), and the interaction of chili and time effects (TreatxTime) on each parameter of autonomic nervous system and the ventilatory response are shown by (A) heart rate (min), (B) systolic blood pressure (mmHg), (C) diastolic blood pressure (mmHg), (D) rMSSD or the square root of mean of sum of square of difference between adjacent RR intervals or successive difference, (E) standard deviation of all normal NN interval, (F) low frequency (normalized unit), (G) low frequency (ms^2), (H) high frequency (normalized unit), (I) high frequency (ms^2), (J) very low frequency (ms^2), (K) low frequency/high frequency ratio, (L) total power (ms^2), (M) expired total ventilation (L/min).



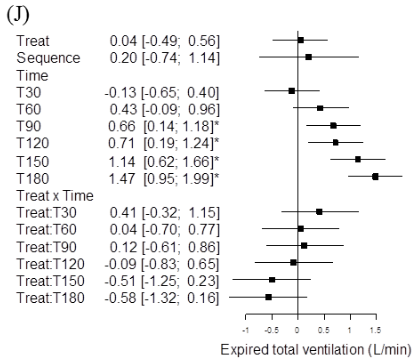


Figure 2 Graphical demonstrations (Forest Plot) of results from the linear mixed (effect) model (LMM) analysis for the chili effects (Treat), the sequence effects (initial allocation to treatment or control), the time effects (6 of 30 minute intervals, T30, T90,…), and the interaction of chili and time effects (TreatxTime) on each parameter of metabolic system are shown by (A) blood sugar (mg/dL), (B) blood insulin (microIU/mL), (C) carbohydrate oxidation (L/min), (D) fat oxidation (g/min), (E) oxygen consumption (L/min), (F) carbon dioxide production (L/min), (G) energy expenditure (Lcal/min), (H) body temperature (^{0}C), (I) respiratory exchange ratio, (J) expired total ventilation (L/min).

overweight worldwide nowadays. Several studies on energy expenditure and substrate oxidation had shown promising results for this effect from chili and capsaicin and even a non-pungent analog, capsiate, could provide an alternative for those who cannot tolerate capsaicin [20]. Nonetheless, the metabolic effects of another capsinoid, synthetic dihydrocapsiate, were found questionable [23], and those of capsaicin and capsiate from meta-analyses were found only at high doses [21]. Despite these inconsistencies, commercial chili products and capsaicin and analogs are already on the markets. In our study, the acute effects on ANS and MS in healthy subjects with a moderate dose of chili (containing 16.96-24.40 mg capsaicin plus 4.86-6.99 mg dihydrocapsaicin) did not support this therapeutic effect. It is known that the long term effects may be different since the responsiveness of cells' receptors involved in the regulation of MS could be modified and many physiologic systems are involved in the adaptation to exposure. Since chili are consumed in daily diets, long term effects from chili will occur in the chili consumers. Although complicated physiologic responses are expected from a long term study, the pharmacological effects of chili or capsaicin are worth to be pursued since chili is a part of daily diets in many countries.

Our LMM statistical analysis found that the time passing after the chili consumption had highly significant effects on both, the sympathetic and parasympathetic nervous systems. The significant increases in heart rate, SBP, and LF (nu) reflecting the increased sympathetic functions whereas the decrease in rMSSD, and HF (nu) reflecting the decreased parasympathetic functions [15]. These responses induced by the time effects were found in this study and this is supported by Lu *et al.* [24] who reported the postprandial changes of the sympathovagal balance measured by HRV. Time passing was found to significantly increase the body's metabolic functions, i.e., blood sugar, blood insulin, carbohydrate oxidation, oxygen consumption, carbon dioxide production, energy expenditure, body temperature, respiratory exchange ratio, and expired total ventilation. The time effects had rarely been described before in previous studies regarding chili effects. This lack of attention to the time effects may be due to experimental designs and statistical models used. Unfortunately, our LMM statistical analysis demonstrated no significant interactions between chili and time effects. This suggests that although chili or time alone had strong effects on the ANS and MS, the shape (but not the location) of the physiologic response curves were similar between the chili and control groups. Our result reflected strong physiologic responses of the body over time which profoundly modulated chili effects. Thus, the final acute responses affected by chili over the 180 min experiments were insubstantial in comparison to the time effects. This result implies that the healthy body's physiology plays a strong part in controlling and adjusting its systems to counter any acute pharmacologic effects of chili, at least, over the experimental period that we monitered.

Conclusion

Our findings confirm that a moderate amount of chili as a food ingredient has significant acute effects on the ANS and MS. However, the human healthy body can control and adjust its physiological parameters to counteract the pharmacologic effects of chili within a short, i.e., 180 min period. Variations of dosage, experimental period, different health conditions, and other pharmacologic parameters should be applied in further studies investigating the effects of chili as a food ingredient.

Acknowledgement

The research was supported by Graduate Study Grants, Science and Technology branch, from the Co-operation of Thailand Research Fund (TRF) and Khon Kaen University.

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