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Thermal Enhancement of Capsaicin on Target Tissue Involved in Hyperthermia

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Abstract

Local thermal enhancement in target tissue is of great interest in tumor hyperthermia. In this study, we proposed a brand-new thermal enhancement protocol for tumor hyperthermia using heat generated from thermogenesis of capsaicin, which can safely deliver a totally localized heating to target tissue. A healthy male volunteer was recruited, whose partial areas of opisthenar and forearm were smeared with 1% (w/w) capsaicin solution, to determine the increase of thermogenesis in local area of human body. In addition, animal experiments on several healthy Kunming (KM) mice (20-22g) were performed to test the feasibility of this capsaicin based thermal enhancement method. Preliminary experiments on the volunteer showed an effective temperature increase in the skin area smeared with capsaicin solution. Animal experiments indicated that distinct enhancement in heating effect presents in the target tissue of mice where capsaicin solution was introduced. The thermal enhancement ability of capsaicin, therefore, suggests that capsaicin can be used as a potential therapeutic adjuvant to locally enhance heating effects in target tissue during tumor hyperthermia.

Index Terms: Thermal enhancement; tumor hyperthermia; capsaicin; thermogenesis

1. Introduction

Regional hyperthermia has long been an important modality of cancer therapy based on the local heating of tumor tissue to above 43°C. Different from the routinely used radiotherapy and chemotherapy, this therapy takes advantage of the high sensitivity of tumor cell to heat, and induces minor side effect which wins its fame as a "Green Therapy". Up to now, a wide variety of hyperthermia modalities have been established such as heating by microwave, ultrasound, radiofrequency, electromagnetic source, laser, and hot medium. However, a common characteristic of these methods is that they will inevitably cause thermal damage to the healthy tissues along the path heat energy is transmitted to the tumor and that surrounding the tumor. Therefore, the ultimate aim of hyperthermia is to optimize the generated temperature distribution within the target tissue such that the tumor is

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essentially heated, but preferably not any healthy tissue surrounding the tumor. For this reason, thermal enhancement on target tissue involved in hyperthermia is necessary. Along this way, the concept of magnetically mediated heating of iron-oxide nanoparticles has received increasing attention as a potential cancer treatment modality [1]. However, this technique is limited by the use of alternating strong electromagnetic field and biological toxic nanoparticles in clinics. In this study, we instead proposed a new physiological approach with little toxicity and side-effect to locally enhance heating effect on target tissue in hyperthermia by adjuvant use of capsaicin.

Capsaicin, the active component of chili peppers, is an irritant for mammals, including humans, and produces a sensation of burning in any tissue with which it comes into contact. It has been used as a biochemical pesticide [2], an adjunct in weight management [3] and an ingredient in cosmetics [4]. Medical research also demonstrated its use in eliminating pain [5] and treating some cancers [6]. As some investigations mentioned, thermoregulation was observed after injection of capsaicin to desensitized rats [7]. In addition, local heat/burning sensation occurred in perineal cutaneous area due to application of capsaicin [8]. Commonly, academic studies associated the thermoregulation and heat/burning sensation by capsaicin with the heat and capsaicin receptor TRPV1, which involves in vasodilatation and increased metabolic rate to change temperature in localized tissue. A recent investigation declared that capsaicin may directly result in thermogenesis [9], which thus indicates that capsaicin might be potentially adjunctive to promote heating effects in hyperthermia. To test the feasibility and efficacy of the capsaicin based thermal enhancement method in hyperthermia, preliminary experimental investigations on human volunteer and animals were performed in this study.

2. Materials and Methods

A. Capsaicin Solutin and Anaesthetic Agent

Because of incomplete solubility of capsaicin, we used Tween-80 in solutions of capsaicin to increase concentration. Finally, 1% (w/w) capsaicin solution was prepared as: 0.1 g crystalline capsaicin firstly was dissolved by 2 to 3 drops of ethanol as well 15 drops of Tween-80, and then diluted to 10 ml with physiological saline solution, which was described by Jancsó [10]; the control solution was correspondingly made merely in absence of crystalline capsaicin. Crystalline capsaicin (purity 80%) and Tween-80 were purchased from the Aladdin Reagent Inc., Shanghai, China.

Crystalline urethane, purchased from the Sinopharm Chemical Reagent Co., Ltd, was dissolved with physiological saline solution to finally make 5% (w/w) urethane solution as anaesthetic agent.

B. Human Test

We recruited a healthy male volunteer (24 years old) to check the direct thermal effect by capsaicin on human being. Local coating of 1 ml capsaicin solution was taken on opisthenar of left hand and two areas of left forearm by absorbent cotton; the right upper limb was locally coated with the control solution using the same method at the corresponding areas.

Temperature transient of such areas were measured at every 20 minutes after coating treatment by FLIR SC620 infrared thermal camera. All thermal images were taken about 2 meters away with the best quality in terms of location and focus, and the surface emissivity was set to 0.98 as the recommendation for biological tissues [11]. The surrounding temperature was about 22 ± 2℃ and humility was 55 ± 5% during the whole experiment. Such values are indispensable parameters for postprocessing of accurate temperature by FLIR R&D Software.

C. Animal Experiments

The Kunming (KM) mouse, an outbred stock derived from Swiss albino mice, is widely employed in Chinese laboratories [12]. All KM mice (20-22 g) used in this study were purchased from the Department of Laboratory Animal Science, Health Science Center, Peking University, China. They were separated by sex and randomly housed every two in specified plastic cages using a layer of wood shavings as bedding, as well as available to commercial diets and water ad libitum.

A single intraperitoneal injection of anaesthetic agent was taken to every mouse at the dose of 2g/kg; and then each one was fixed on a board and shaved on abdomen and chest for ruling out disorders caused by hairs in infrared images. The capsaicin solution was injected subcutaneously at a dose of 0.1 ml or topically smeared on the abdomen to mice with absorbent cotton which had been immersed in the capsaicin solution in advance. After application of capsaicin solution or control solution, the mice were observed for 100 minutes and then heated on that daubed region by 808nm near infrared radiation at power of 2W and 5 centimeters away for over 3 minutes, so as to determine the thermal enhancement of capsaicin on target tissue in hyperthermia.

The method of observation was the same as above mentioned. Firstly, we captured the thermal images of shaved mice merely influenced by capsaicin about half a meter away with its best quality every 20 minutes; then, we photographed the heating process, with capsaicin solution or with control solution, every 10 seconds.

3. Results and Discussion

We definitely expect to obtain directly capsaicin-induced thermal enhancement in hyperthermia, but it may be dangerous to manipulate the heating directly on human with little information about that. In this study, instead, we took a safe experiment without heating on human, as well as real heating experiments on animal with near infrared radiation. The results for the case of human volunteer test were given in Tab. Ⅰ and Fig. 1; so were the results for the case of mice depicted in Figs. 2-5.

The thermal images on locally capsaicin-applied opisthenar (Position 1), forepart of forearm (Position 2) and posterior of forearm (Position 3) of a volunteer's left upper limb with time can be found in Fig. 1. It can be visually concluded that temperatures of regions applied with capsaicin solution are clearly higher than those of surrounding areas, and that the transient warming effect diffused to surrounding tissues, which probably because capsaicin permeated skin and flowed in the vein and blood capillary.

The average temperatures of such positions with time were showed in Table 1. It showed that skin temperature of all these three positions increased in the first half hours and then leveled off afterward, and that results on positions of forearm boosted more quickly and intensively than that of opisthenar, probably because obviously blood flow under the skin of opisthenar reduced the accumulation of capsaicin and thereby attenuated the capsaicin-induced thermal effects. The same volunteer with control solution applied on the corresponding sites of the other arm and hand showed on dramatic temperature variation with time.

Table 1 Temperature of Skin Subjected to Local Coating of Capsaicin Solution

Position	Average Skin Temperature (℃)			
	0 min	20 min	40 min	60min
Position 1 (Opisthenar)	33.5	33.7	35.1	35.1
Position 2 (Forepart of Forearm)	33.3	34.5	35.4	35.4
Position 3 (Posterior of Forearm)	33.4	34.9	35.5	35.5

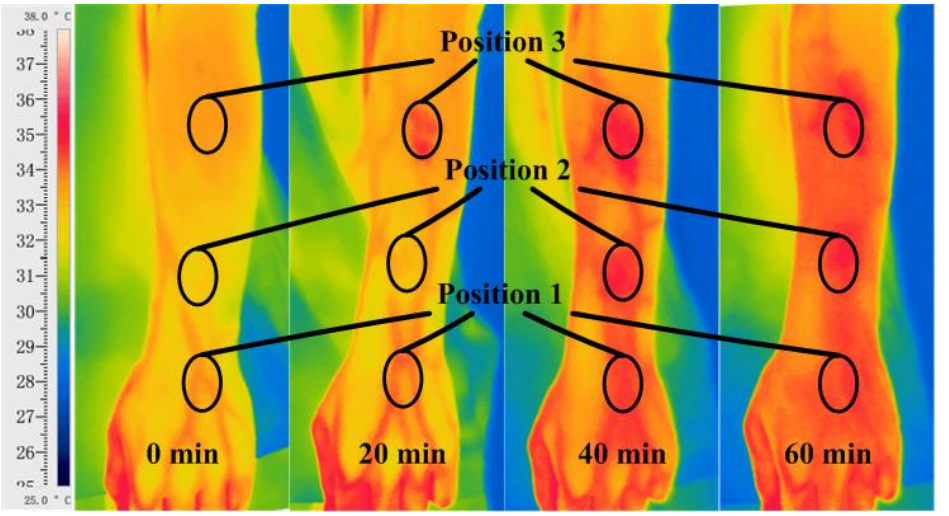

Fig. 1 Transient thermal image of opisthenar and forearm.

As state above, capsaicin-induced skin warming is prominent on skin, and the heat/burning sensation occurred as previous studies mentioned [8]. It also concluded that the thermal effect was attenuated by blood flow due to its transportation. The energy brought on the warming presumably came from that capsaicin stimulated uncoupled ATP hydrolysis, which could result in thermogenesis unremittedly in muscle cells [9].

Two KM mice (1 male and 1 female), anaesthetized by prepared anaesthetized agent, combined with applying control solution, gradually decreased in body temperature by about 0.1 to 0.2℃ every ten minutes. Another two anaesthetized KM mice (1 male and 1 female) both appeared an obviously further fall of surface temperature on abdomen after a single subcutaneous injection of 0.1 ml prepared capsaicin solution. The male mice died after this experiment due to a longtime reduction of body temperature. This hypothermia agreed with previous study in unsensitized rats [7]. Consequently, the subcutaneous injection method may not be feasible; at least it is not suitable in mice.

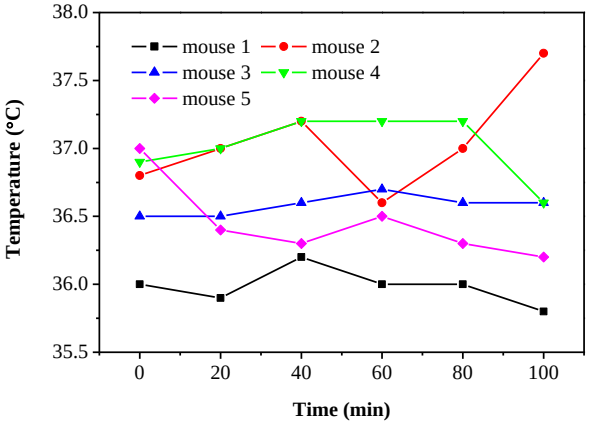

Fig. 2 Skin temperature response after coating with capsaicin

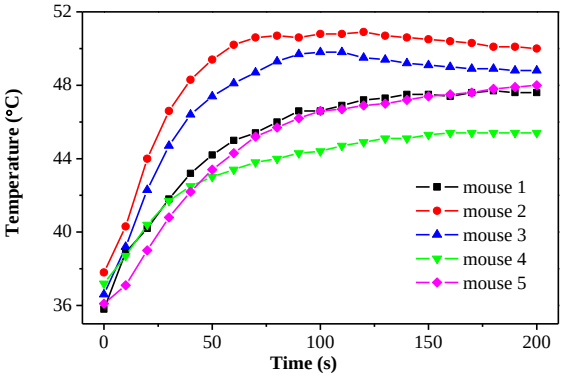

Fig. 3 Thermal enhancement by heating

Six anaesthetized KM mice (3 males and 3 females) daubed with capsaicin solution. The initial surface temperature of one female was unusual high (38.3℃), and the experimental results about this mouse were therefore not presented. Fig. 2 depicted the observation of the remained five mice (three males and two females) in about 100 minutes. It indicated that the basal body temperature varied in mice from 36.0 to 37.0℃, and that the average abdominal temperature of each mouse fluctuated lightly around its basal body temperature in the first 60 minutes. Later, mouse 2 increased markedly, mouse 3 still fluctuated slightly, mouse 1 and mouse 5 began to decrease slightly, and mouse 4 reduced dramatically. That may attribute to that capsaicin started to lose its efficacy in mouse 1, 4 and 5, but still in work in mouse 2 and mouse 3.

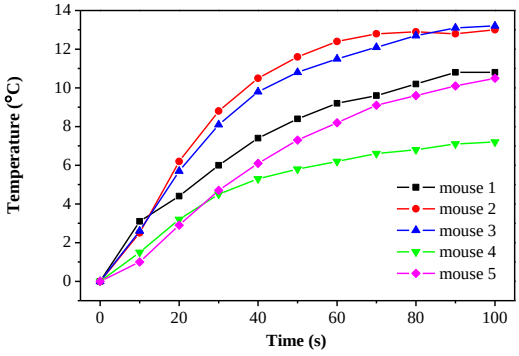

Fig. 4 Accumulation of previous time interval from initial skin temperature due to heating for the first 100 seconds

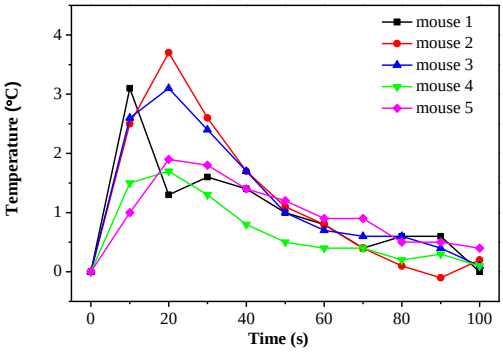

Fig. 5 Difference of skin temperature between every time interval due to heating for the first 100 seconds

Afterward, all these five locally smeared mice were heated by near infrared radiation with the manipulation described above. Fig. 3 showed the thermal enhancement. It depicted that mice with capsaicin still working (mouse 2 and 3) increased more sharply in temperature, especially in the beginning, than those with capsaicin losing their efficacies (mouse 1, 4 and 5), and that the extent of augment was related to the remained intensity of capsaicin-induced thermal effect. The heating behavior in mouse 4 was almost the same as those in mice during experiment that four mice was heated by such near infrared radiation with applying control solution after anaesthetized. It thereby confirmed our hypothesis that capsaicin can work well in thermal enhancement on target tissues in hyperthermia.

Furthermore, Fig. 4 indicated that the accumulation of previous temperature differences from the initial temperature augmented significantly in the first 100 seconds. It confirmed the former conclusion (made from Fig. 3) that thermal enhancement in mouse 2 and 3 (capsaicin still in work) are greater than those in mouse 1 and 5 (capsaicin began to lose efficacy), as well as further greater than mouse 4 (capsaicin had lost efficacy markedly). It can also be found from Fig. 5 that the peaks of temperature in mouse 2 and 3 are higher than those in mouse 1 and 4, even mouse 5, in the first 40 seconds.

In clinics, how to enhance thermal effect on biological tissues is one of the basic objectives in hyperemia. Clearly, the results in this study suggest that capsaicin, locally smeared in a volunteer, worked well in temperature warming, and that the combined method of capsaicin-induced heat and heating by external device, manipulated in mice, remarkably demonstrated the thermal enhancement. Thus, the adjuvant use of capsaicin is feasible. Though the thermal enhancement is confirmed, there are unresolved problems that the diffusion either in tissues or in blood is now uncontrollable and the time when capsaicin began to work or lose its efficacy is indeterminate.

4. Conclusion

An effective approach to enhance heating effects on treatment of tumors in hyperthermia by adjuvant use of capsaicin was proposed in this study. Through experimental investigations on temperatures of localized skin in a volunteer merely applied capsaicin solution in low concentration, as well on abdominal skin in mice locally applied with the same capsaicin solution, with or without being subjected to near infrared radiation, the feasibility of the capsaicin based thermal enhancement method was demonstrated. The results indicate that this novel local application of capsaicin can increase cutaneous temperature, and that adjuvant use of capsaicin combined with heating can serve as an applicable way to significantly enhance the heating effects of biological tissues during hyperthermia. The present work might be the basis to find a new effective modality for thermal enhancement in hyperthermia.

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