Effects of Administration with BQ 788 on Heat Stroke in Rats

Tasi Hsiu Yang¹  Mei Fen Shih²  Mei Ying Wang³  Wen Yueh Ho³  Mei Lin Tsai³  Kuen Lin Leu³  Mao Tsun Lin⁴  Chia Chyuan Liu³*

¹Department and Institute of Health and Nutrition,
²Department of Pharmacy,
³Department and Institute of Cosmetic Science,
- Chia-Nan University of Pharmacy and Science,
  Tainan, Taiwan 71710, R.O.C.
⁴Department of Medical Research, Chi-Mei Medical Center, Tainan, Taiwan

Abstract

Heat stroke was induced by placing urethane-anesthetized rats in the hot chamber with 42°C ambient temperature. Instead, the normothermic control rats were placed in chamber with room temperature, 24°C. The onset of the rapidly decreased mean arterial pressure (MAP) and cerebral blood flow (CBF) from peak level was defined as the onset of heat stroke. And the interval from the onset of heat stroke to cardiac arrest was defined as the survival time (ST) of rats. The values of MAP and CBF after heat stroke onset were significantly lower than those in control rats. However, plasma levels of tumor necrosis factor-α (TNF-α) were higher. Extracellular concentration of glutamate and lactate/pyruvate ratio (cellular ischemia markers), and glycerol (a cellular injury marker) in the corpus striatum were markedly greater. The role of ET-1 in the pathological manifestations of heat stroke is worth further study. Effects following endothelin B (ETB) receptor activation (but not ETA receptor) by ET-1 on cytokine production of human monocytes with 7-fold higher release of TNF-α, compared to another cytokines. There were sufficient evidences to show that high levels of TNF-α not only resulted multi-organ dysfunction via inflammatory response and led to shorten the survival time of heat stroke animals, but were closely associated with cardiac function in various cardiovascular disorders. Additionally, there was less attention to clarify in detail the effective on heat stroke with ETBR antagonists. Therefore, in present study, we attempted to investigate effects of acute treatment or pretreatment with an ETBR antagonist (BQ 788) on heat stroke-induced pathophysiologic changes (including arterial hypotension, cerebral ischemia, and neuronal damage) and survival in a rat model. In present study, our results suggest that heat stroke induced low SBF, high levels of plasma TNF-α, arterial hypotension, cerebral ischemia, neuronal damage, and a decrease in survival time in rats. We tried to give BQ 788 immediately or beforehand, and expect to be able to improve the heat stroke-induced arterial hypotension, cerebral ischemia, and neuronal damage, and eventually resulted in prolongation of the survival time; however, ETBR antagonist, showed no efficacy in those lesions and symptoms. Our investigations implicate that the pretreatment or treatment with ETBR may have no efficiency to diminish the damage and pathological formation of heat stroke in a rat model.

Keywords: Heat stroke; Cerebral Ischemia; Cerebral Neuronal Injury; Endothelial injury; BQ 788.

*Correspondence: Department and Institute of Cosmetic Science, Chia-Nan University of Pharmacy and Science, Tainan, Taiwan 71710, R.O.C.
Tel: +886-6-2664911 (ext. 2419).
Fax: +886-6-2667324
E-mail: ccliu@chna.edu.tw (C. C. Liu)
Introduction

Heat stroke, a common and extremely mortal disease, was easily happened in the tropic country that had high environmental temperature. The regular syndromes of heat stroke were central nervous system (CNS) dysfunction including delirium, convulsion, or coma (Yaqub et al., 1986; Khogali & Weiner, 1980; Austin & Berry, 1956). In spite of many studies tried variously therapeutic strategies to improve the damage induced by heat stroke; however, there was no one could be effective to completely improve until now and the truly mechanism of heat stroke-induced injury remain unclear. There was evidence that cerebral ischemia (due to arterial hypotension), rather than hyperthermia, was the main reason for the onset of heat stroke (Lin & Lin, 1992; Lin et al., 1997; Bouchama et al., 1991a). Heat stroke-evoked multiorgan injury and neural damage were thought to have pivotal relationship with high levels of cytokines, endotoxin, and intracranial hypertension (Gathiram et al., 1988; Bouchama et al., 1991b; Hall et al., 2001). Studies in animal models had been shown that heat stroke induces systemic and local (CNS) production of tumor necrosis factor-alpha (TNF-α) (Bouchama et al., 1991b; Bouchama et al., 1993; Niu et al., 2003). Medications for blocking effect of cytokines, which were given to animals before heat stroke, could attenuate neurological injury, prevent arterial hypotension and improve survival time (ST) of rats (Liu et al., 2009; Bouchama & Knochel, 2002; Kuo et al., 2003).

According to scientific literatures, the patients and the animals of many cerebral diseases such as stroke, brain trauma, and cerebral ischemia were found marked increased the plasma or brain endothelin-1 (ET-1) levels compared to the normal (Fujimori et al., 1990; Kraus et al., 1991; Suzuki et al., 1992). Topical ET-1 can reduce cerebral blood flow, increase the inflammatory response, and induce neuronal damage. ET-1, one of endothelin isopeptides, was a potent vasoconstrictor and acted on endothelin-A receptor (ETAR) and endothelin-B receptor (ETBR) receptor to achieve the biological effects (Luscher & Barton, 2000). In 1996, Bouchama et al. observed that endothelial cells were activated/injured in heat stroke patients and indicated these changes can mediate certain aspects of the pathophysiology in heat stroke (Sohal et al., 1968; Chao et al., 1981; Bouchama et al., 1996). Thus, it is likely that ET-1 mechanisms are involved in the pathogenesis of heat stroke. The development of ETA and ETB selective receptor antagonists (Luscher & Barton, 2000), which can be administrated intravenously in rats with heat stroke, has made it possible to elucidate this issue.

Additionally, the previous results (Ruetten & Thiemermann, 1997) have shown that the generation of TNF-α by cells activated with ET-1 points to a pro-inflammatory role of ET-1 in heart failure or circulatory shock, which are associated with high ET-1 plasma levels. Our previous studies also indicated that the plasma levels of TNF-α are shown to be well related to the severity of heat stroke (Yang et al., 2010). Indeed, increased systemic levels of TNF-α are associated with heat stroke-induced arterial hypotension, cerebral ischemia, and neuronal damage (Yang et al., 2010). Consequently, recent studies have shown that effects following ETB receptor activation (but not ETA receptor) by ET-1 on cytokine production of human monocytes with 7-fold higher release of TNF-α compared to another cytokines (Juergens et al., 2008). Meanwhile, there was less attention to clarify in detail the effective on heat stroke with ETBR antagonists. Therefore, in present study, we attempted to investigate effects of acute treatment or pretreatment with an ETBR antagonist (BQ 788) on heat stroke-induced...
pathophysiologic changes (including arterial hypotension, cerebral ischemia, and neuronal damage) and survival in a rat model.

**Materials and methods**

**Experimental animals**—Adult male Sprague-Dawley rats weighing between 270 and 320 g were obtained from the Animal Resource Center, National Science Council of Republic of China (Taipei, Taiwan, ROC). Between experiments the animals were housed individually at an ambient temperature of 24±1 °C with a 12-h light-dark cycle, with the lights being switched on at 0600 h. Animal chow and water were allowed *ad libitum*. All protocol were approved by the Animal Ethics Committee of the Chia-Nan University of Pharmacy and Science, Tainan, Taiwan (approbated no. CN-IACUC-96032) in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and the guidelines of the Animal Welfare Act.

**Animal surgery and physiological parameter monitoring**—The right femoral artery and vein of rats will be cannulated, under urethane anesthesia (1.4 g/kg, i.p.), with polyethylene tubing (PE50) for blood pressure monitoring, blood sampling and drug administration. The animals will be positioned in a stereotaxic apparatus (Kopf model 1460). Physiological monitoring included colon temperature (Tco), mean arterial pressure (MAP), heart rate (HR), the temperature of brain and cerebral blood flow (CBF) values in the corpus striatum. Colon temperature will be monitored continuously by a thermocouple.

**Induction of heat stroke and study experiment design**—Each rat was randomly assigned to several groups. One group of rats (n=6) with heat stroke received no treatments. Heat stroke was induced by exposing the animals to an ambient temperature of 42 °C (with a relative humidity of 60% in a temperature-controlled chamber). The moment in which MAP and local CBF began to decrease from their peak levels was taken as the onset of heat stroke. Another six group of rats (n=6) with heat stroke respectively received intravenous treatment with normal saline (NS) 1 ml/kg b.w. via femoral vein, vehicle solution (1 ml/kg b.w., i.v., 0.5% DMSO in normal saline), treatment with BQ 788 (0.1 ml/kg b.w., i.v., an ETB receptor antagonist; Phoenix Pharmaceuticals, Inc., Mountain View, CA, USA), treatment with BQ 788 (0.5 ml/kg b.w., i.v.), pretreatment with BQ 788 (0.1 ml/kg b.w., i.v.), and pretreatment with BQ 788 (0.5 ml/kg b.w., i.v.). Another group of rats (n=6) were normothermia, control rats which were exposed to an ambient temperature of 24 °C for at least 90 min to reach thermal equilibrium. In addition, the rats intravenous treatments with NS or vehicle solution via femoral vein at the normothermic condition were also assess in these physiologic parameters. Their colon temperatures were maintained at about 36.0 °C using the electric thermal mat before the start of experiments. The rats of these groups were continually monitored the physiological parameter (such as Tco, MAP, HR, and CBF) and survival time (interval between the onset of heat stroke and animal death) during heat stroke.

**Cerebral blood flow monitoring**—Local cerebral blood flow (CBF) in the corpus striatum was monitored with a Laserflo BPM2 laser Doppler flowmeter (Vasametics, St. Paul, NM, USA). A 24 gauge stainless steel needle probe (diameter, 0.58 mm; length, 40 mm) was inserted into the right corpus striatum using the coordinates of A, interaural 9.7 mm; L, 2.0 mm from midline; and H, 4.5 mm from the top of the skull. The needle then was connected to the Yokogawa DR130 thermocouple to measure brain temperature.

**Measurement of extracellular ischemia**
A microdialysis probe (4 mm in length: CMA/12. Carnegie Medicine, Stockholm, Sweden) was stereotaxically implanted into the left corpus striatum. An equilibrium period of 60 min without sampling was allowed after probe implantation. The microdialysis was perfused at 2.0 \( \mu \text{l./min} \), and the dialysates were sampled in microvials. The dialysates were collected every 10 min in a CMA/140 fraction collector. Aliquots of dialysates (5 \( \mu \text{l} \)) were injected onto a CMA 600 microdialysis analyzer for measurement of lactate, glycerol, pyruvate, and glutamate as described previously (Liu CC et al., 2009; Yang et al., 2010).

**Assay for plasma TNF-\( \alpha \)***  Blood samples were taken at 95 min after heat exposure for determination of TNF-\( \alpha \) levels. Blood samples were allowed to clot for 2 hours at room temperature or overnight at 2-8 \( ^\circ \text{C} \) before centrifuging for 20 minutes at approximately 2000\( \times\)g. Serum was quickly removed from these plasma samples and assayed for TNF-\( \alpha \) immediately. The DuoSet ELISA Development System rat TNF-\( \alpha \) kit (R\&D Systems, Minneapolis, MN, USA) was used for measuring the levels of active rat TNF-\( \alpha \) present in plasma. This assay employs the quantitative colorimetric sandwich Enzyme-Linked Immunosorbent Assay (ELISA) technique. The assay was based on the competition between rat TNF-\( \alpha \) in the test sample and enzyme-liked recombinant rat TNF-\( \alpha \) for binding sites on a specific TNF-\( \alpha \) primary antibody. An affinity purified antibody specific for rat TNF-\( \alpha \) had been pre-coated onto a microplate. Standards, Controls, and samples are pipetted into the wells and any rat TNF-\( \alpha \) present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polycloned antibody for rat TNF-\( \alpha \) is added to the wells. Following a wash to remove any unbound antibody-enzyme reagents, a substrate solution is added to the wells. The enzyme reaction yields a blue product that turns yellow when the Stop Solution is added. After the addition of stop solution, plates were read in an ELISA plate reader at 450 nm.

**Statistical analysis***  Data are the mean\( \pm \)S EM. Repeated-measures analysis of variance was used for factorial experiments, whereas Duncan’s multiple-range test was used for post hoc multiple comparisons among means. The criteria for statistical significance was set at \( p<0.05 \). Neuron damage scores were analyzed using Kruskal-Wallis test. The \( p \) value less than 0.05 was considered as statistically significant.

**Results and Discussion**

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Survival time (min)</th>
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<tbody>
<tr>
<td>1. Rats treated with NS and kept at 24°C</td>
<td>&gt; 480</td>
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<tr>
<td>2. Rats treated with NS (1 ml/kg, i.v.) and kept at 42°C</td>
<td>22±3*</td>
</tr>
<tr>
<td>3. Rats treated with vehicle solution (1 ml/kg, i.v.) and kept at 42°C</td>
<td>21±4*</td>
</tr>
<tr>
<td>4. Rats pretreated with vehicle solution (1 ml/kg, i.v., 0 min before HE) and kept at 42°C</td>
<td>26±5*</td>
</tr>
<tr>
<td>5. Rats treated with BQ788 (0.1 ml/kg, i.v.) and kept at 42°C</td>
<td>24±4*</td>
</tr>
<tr>
<td>6. Rats treated with BQ788 (0.5 ml/kg, i.v.) and kept at 42°C</td>
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<td>23±3*</td>
</tr>
<tr>
<td>8. Rats pretreated with BQ788 (0.5 ml/kg, i.v., 0 min before HE) and kept at 42°C</td>
<td>24±5*</td>
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</table>

Values are the mean SEM of 3 rats per group. Groups 2-8 exposed to 42°C had heat exposure withdrawn at the onset of heat stroke. *\( p<0.05 \), compared with the corresponding control values (rats kept at 24°C). (one-way ANOVA, followed by Duncan’s test).

As shown in Table 1, the values of survival time (ST) in heat stroke rats treated with normal saline (NS) and vehicle solution via femoral vein were respectively 22±3 and 21±4 minutes, no difference in rats treated with NS group and vehicle solution group. Similarly, the ST in heat stroke rats between treatment and pretreatment with vehicle solution groups has no significant differences. In
acute treatment with BQ 788 groups, no matter rats treated with 0.1 ml/kg or 0.5 ml/kg, the survival time of rats were revealed similarly in these groups. The values of ST in immediate treatment with BQ 788 at the onset of heat stroke in 0.1 ml/kg and 0.5 ml/kg groups were respectively 24±4 and 21±4 minutes. As to pretreatment with BQ 788 at 0 min before heat exposure, the ST in 0.1 ml/kg and 0.5 ml/kg groups was also shown no apparent changes, compared to acute treatment with NS, vehicle solution, or BQ 788 groups. Hence, our present results showed that acute treatment or pretreatment with BQ 788 have no influence on ST of heat stroke in rats.

Figure 1 showed the effects of heat stress on Tco, MAP, heart rate (HR), and local striatal blood flow (SBF). The values of Tco were significantly higher in rats 20-40 minutes after the onset of heat stroke than in those of preheat stress. On the other hand, the values of MAP, HR, and SBF were apparently lower in rats after the onset of heat stroke. It was found that the heat stroke-induced arterial hypotension and decrement of SBF was no significant difference by no matter treatment with BQ 788 immediately at the onset of heat stroke or pretreatment with BQ 788 before the onset of heat stroke (at 0 min before heat exposure) in rats (as shown in figure 1). Besides, in the NS or vehicle solution-treated groups, rats after heat stroke displayed severe cerebral ischemia and cerebral neuronal damage by CMA 600 microdialysis analyzer for measurement of lactate, glycerol, pyruvate, and glutamate, compared with those of normothermic control rats (Figure 2). The lactate/pyruvate ratio is a well-known marker of cell ischemia, that is, an inadequate supply of oxygen and glucose (Hillered & Persson, 1999; Hillered et al., 1990).
Glutamate is released from neurons during ischemia and initiates a pathological influx of calcium leading to cell damage. It is an indirect marker of cell damage in the brain (Nilsson et al., 1996; Persson & Hillered, 1992). As shown in figure 2, it seems to have no effective on amelioration of heat stroke-induced high levels of glutamate, glycerol, and pyruvate/lactate ratio in corpus striatum of rats.

Evidences had been accumulated to indicate that endogenous ET-1 levels were increased in the plasma and cerebrospinal fluid (CSF) of patients with cerebral ischemia, hypertension, stroke, or brain trauma (Fujimori et al., 1990; Kraus et al., 1991; Suzuki et al., 1992). Recently, the pathophysiological role of ET-1 was extensively investigated in many cardiovascular diseases such as ischemic heart disease, stroke and cerebral ischemia (Matsuo et al., 2001; Schiffrin, 2001; Russell & Molenaar 2000). Previous studies have elucidated that ET-1 was well associated with some of the mechanisms involved in the vascular damage induced by endothelin, and these include increased oxidative stress, stimulation of NF kappaB, upregulation of vascular cell adhesion molecules and chemoattractant peptides, results in the growth and inflammatory responses (Muller et al., 2000; Nicoletti & Michel, 1999). In these experimental models, endothelin receptor antagonists regressed vascular growth and inflammation, and improved endothelial dysfunction (Schiffrin, 2001). Similarly, the amount of ET-1 in both cerebral tissue and plasma were also increased after cerebral ischemia (Bian et al., 1994). After middle cerebral artery occlusion (MCAO), the high levels of ET-1 were thought to enhance permeability of blood-brain barrier (BBB) and to mediate in pathogenesis of brain edema (Chi et al., 2001); however, the ETR antagonists are known to exert a protective effect against the ischemic damage induced by MCAO, brain trauma, and stroke (Matsuo et al., 2001; Barone et al., 2000). So far, the pathophysiological role of ET-1 in rats with heat stroke doesn’t completely understand very well. However, we implicate that high plasma levels of ET-1 may mediate in progress of pathophysiological formation in rats with heat stroke, and try to obstruct the effect of ET-1 by systemic pretreatment of ETBR antagonist, and to improve the heat stroke-induced damage and prolong the survival time. Studies were found that endothelial cell activation/injury occurred in heat stroke victims and probably involved in pathologic manifestations of heat stroke (Sohal et al., 1968; Chao et al., 1981; Bouchama et al., 1996), indeed, in our previous study, rats after heat stroke revealed the elevated levels of plasma ET-1 and have deeply associated with the increased systemic inflammatory response (high TNF-\(\alpha\) levels in plasma). The previous studies indicated that the ET-1-mediated expressions of cytokines production were mainly related to the ETB receptor activation in some inflammatory response formation of diseases (Juergens et al., 2008; Filipovich et al., 2008). Additionally, although the previous study had ever investigated effects of the high systemic ET-1 levels on heat stroke and obtained the endothelial cell activation/injury in heat stroke victims and animals, there was less attention on the effects of ETBR antagonists in detail in a rat model of heat stroke.

The present study has shown that heat stroke evoked arterial hypotension, cerebral ischemia and neuronal damage, and elevated TNF-\(\alpha\) level in anesthetized rats (figure 2 and 3). These results are in good agreement with those of Bouchama et al. (Bouchama et al., 1991b; Bouchama et al., 1993) and Lin et al. (Lin et al., 1997) who have also shown that the concentration of circulating endotoxins and
pyrogenic cytokines was elevated in heat stroke patients or animals. Increases in concentration of these pyrogenic cytokines can cause increased production of hypothalamic arachidonic acid metabolites and thereby raise the hypothalamic set-point (Hammami et al., 1997). Besides, the plasma concentrations of inflammatory cytokines (such as TNF-α) is elevated in people and animals with heat stroke (Bouchama et al., 1991b; Hammami et al., 1997). The concentration of TNF-α correlates well with the severity of heat stroke (Liu et al., 2009; Yang et al., 2010). Our previous studies have also shown that heat stroke induces systemic and local (central nervous system) production of TNF-α in rats (Niu et al., 2003; Kuo et al., 2003). Indeed, an increase in the levels of these inflammatory cytokines is associated with arterial hypotension, high intracranial pressure, cerebral ischemia and injury. A complicated interplay among the acute physiological alterations of heat stroke well related with the direct cytotoxicity of heat, the inflammatory responses of the host, and hyperthermia (e.g., circulatory failure, hypoxia, and increased metabolic demand). These alterations progressively became multiorgan-dysfunction syndrome and the damage of heat stroke (Bouchama et al., 1996; Grogan & Hopkins, 2002; Ruetten & Thiemermann, 1997). Bouchama et al. indicated that a systemic inflammatory response led to a syndrome of multiorgan dysfunction in which encephalopathy predominates (Bouchama & Knochel, 2002). High concentration of cytokines was thought to not only associate with the above-mentioned damage of heat stroke but also involve in heat stroke-induced cardiovascular dysfunction (Ruetten & Thiemermann, 1997; Knochel, 1989). High levels of plasma TNF-α certainly played an important role in pathophysiological formation of many cardiovascular diseases (Lin et al., 1995; Lin et al., 1994). For instance, Nakamura et al. suggested that TNF-α might play pathophysiological roles in the
progression of acute heart failure (Nakamura et al., 2002; Stumpf et al., 2003). Besides that, earlier studies had indicated that systemic administration of TNF-\(\alpha\) to animals could produce a syndrome similar to septic shock (Schirmer et al., 1989).

In summary, heat stroke induced low SBF, high levels of plasma TNF-\(\alpha\), arterial hypotension, cerebral ischemia, neuronal damage, and a decrease in survival time in rats. We attempted to give ETBR antagonist immediately or beforehand, and expect to be able to improve the heat stroke-induced arterial hypotension, cerebral ischemia, and neuronal damage, and eventually resulted in prolongation of the survival time; however, ETBR antagonist, showed no efficacy in those lesions and symptoms. Our investigations implicate that the pretreatment or treatment with ETBR may have no efficiency to diminish the damage and pathological formation of heat stroke in a rat model.

References
10. Chi, O. Z., Liu, X., & Weiss, H. R. Effects of


40. Ruetten, H. & Thiemermann, C. Combination immunotherapy which neutralises the effects of TNF alpha and IL-1 beta attenuates the circulatory failure and multiple organ dysfunction caused by endotoxin in the rat. J.Physiol Pharmacol. 48, 605-621, 1997.


對熱中風大鼠投予 BQ 788 處理之影響

楊彩秀¹ 施美份² 汪梅英³ 何文岳³ 蔡玫琳¹ 吕昆霖³ 林茂村⁴ 刘家全³*

¹嘉南藥理科技大學保健營養系
²嘉南藥理科技大學藥學系
³嘉南藥理科技大學化粧品應用與管理系
⁴奇美醫學中心醫學研究部

摘要

將 urethane 麻醉後大鼠置於 42°C 雲箱中誘發熱中風之生成,而常溫控制組大鼠則置於室溫 24°C 的
溫箱中。當熱中風誘發生成過程中,大鼠平均動脈壓和腦血流數值從至高點瞬間滑落之時間點,視為熱
中風生成點,而從熱中風生成點起至大鼠心跳停止的期間則視為熱中風存活時間。大鼠的平均動脈壓和
腦血流數值於熱中風生成後顯著的比常溫控制組大鼠低落,而血漿中腫瘤壞死因子-α (TNF-α) 則明
顯升高,於腦中紋狀體中胞外麩胺酸和丙酮酸/乳酸比值 (細胞缺血指標)和甘油 (細胞損傷指標)顯著上升。
內皮素-1 於熱中風病理生成過程被認爲是值得深入探討的。研究指出於人體單核球中內皮素-1 作用生成
細胞介質素,主要是透過內皮素 B 受體的作用 (而非內皮素 A 受體),且相對於其他細胞介質素生成,可
誘發產生七倍高的 TNF-α。有許多證據也指出於熱中風動物體中高濃度的 TNF-α 不僅會透過發炎反應
導致多發性器官功能失調,而會縮短熱中風存活時間,並且在許多心血管疾病中與心臟功能有密切關係。另有,
也鮮少有針對內皮素 B 受體拮抗劑對熱中風之影響的詳細研究。因此,現今的實驗中,我們試圖
探討給大鼠急性投予和前處理內皮素 B 受體拮抗劑 (BQ 788)對熱中風所致生理病理改變 (包括動脈壓低
落、腦缺血與神經損傷) 之影響。現今研究中,結果我們發現大鼠熱中風生成後呈現低腦血流、高血漿濃度
TNF-α、低動脈壓、腦缺血及損傷情形,最後導致存活時間縮短。我們嘗試以 BQ 788 立即
與事先投予大鼠,期望可改善熱中風所致動脈圧、腦缺血及損傷情形,且可延長存活時間。然而, B
受體拮抗劑給予似乎並無法有效的減輕或改善熱中風傷害。而我們目前的研究結果發現, 鍾對大鼠熱中
風的動物模式,不管急性或預先投予大鼠內皮素 B 受體拮抗劑皆無法有效的減輕或改善熱中風症狀和病
理發展。

關鍵詞: 熱中風; 腦缺血; 腦神經損傷; 內皮細胞受損; BQ 788

*通訊作者:嘉南藥理科技大學化粧品應用與管理系
Tel: +886-6-2664911 (ext: 2419)
Fax: +886-6-2667324
E-mail: ccliu@chna.edu.tw (C. C. Liu)