行政院國家科學委員會補助專題研究計畫成果報告

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※ Adenosinergic modulation of ventilation and maximal ※
※ exercise capacity in obesity ※
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計畫編號：NSC　90－2314－B－040－022
執行期間：　90 年　12 月 15 日至　91 年 7 月 31 日

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□出席國際學術會議心得報告及發表之論文各一份
□國際合作研究計畫國外研究報告書一份

執行單位：中山醫學大學

中　華　民　國　91　年　09　月　24　日

行政院國家科學委員會專題研究計畫成果報告

在肥胖症中 adenosine 對呼吸和運動最大耗氧量的調節

Preparation of NSC Project Reports

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中文摘要

這研究是為了調查在基因肥胖鼠中，是否改變 adenosine 的神經調節會影響肥胖不正常的換氣反應和肥胖不足的運動能力。 8 隻瘦的基因瘦鼠和 8 隻胖的基因肥胖鼠被研究。用全身體積-壓力變化法（barometric method）來量測正常的換氣反應和 5 分鐘 7%二氧化碳的換氣反應。用代謝功能測試跑步機（metabolic treadmill）來量測最大運動耗氧量。這兩種換氣和運動的測量皆進行三次重複的測試，測試前隨機的給予等量已緘封的三藥劑之一，其三藥劑包括生理食鹽水、8-（p-sulphophenyl）-theophylline（ 8-PST, 8 mg/kg,周圍系統 adenosine 接受體的阻斷劑）或 aminophylline（AMPH, 15 mg/kg, 中央和周圍系統 adenosine 接受體的阻斷劑）。在正常的換氣反應和二氧化碳的換氣反應，AMPH 有意義的增加換氣量在基因瘦和胖鼠。在運動反應，AMPH 有意義的增加基因胖鼠的最大運動耗氧量但不增加基因瘦鼠的最大運動耗氧量。相反的 8-PST 沒有改變換氣量和最大運動耗氧量在基因瘦和胖鼠。我們的發現顯示在基因胖鼠中沒有改變的 adenosine 機制影響正常的換氣反應和二氧化碳的換氣反應。相反的改變的 adenosine 的機制位於中央神經系統部分導致在肥胖症中運動能力的不足。

關鍵詞：adenosine，**呼吸，運動，肥胖**

Abstract

This study was designed to investgate whether altered adenosinergic mechanisms contribute to regulate ventilation and influence exercise capacity in obese Zucker (Z) rats. Eight lean and eight obese male Z rats were studied. Ventilation at rest and ventilation during 5 min hypercapnic (7% CO2) challenges were measured by the barometric method. Peak oxygen consumption (VO2 peak) in response to a progressive treadmill test to exhaustion was measured in a metabolic treadmill. Ventilation and VO2 peak were assessed following the randomized blinded administration of equal volumes of saline (control), 8-(p-sulphophenyl)-theophylline (8-PST, 8 mg/kg, peripheral adenosine receptor antagonist), or aminophylline (AMPH, 15 mg/kg, peripheral & central adenosine receptor antagonist). During room air breathing and hypercapnic exposure, AMPH significantly ($P<0.05$) increased VE in both lean and obese rats. During exercise test, AMPH selectively increased VO2 peak in obese but not lean rats. In contrast, 8-PST failed to alter ventilation and VO2 peak in both lean and obese rats. Our findings imply that the altered adenosinegic modulation of ventilation during room air and hypercapnic exposure were not found in obese Z rats whereas the altered adenosinergic mechanisms acting specifically on receptors located within the central nervous system are partially responsible for the reduced peak oxygen consumption in obese rats.

Keywords: adenosine, respiration, exercise, obesity

Introduction:

The obese Zucker (Z) rats presents many of the same deficits as noted in obese humans including blunted ventilatory responses, and poor exercise capacity (1, 2). Adenosine, a purine nucleoside product of ATP

metabolism, functions as a neuromodulator in the peripheral and central nervous systems. Endogenous adenosine is involved in a wide range of physiological responses including the regulation of ventilation and energy balance (3).

The activity of adenosine receptors in obese rats and mice is highly active, especially in adipose cell (4). The role of adenosine in mediating breathing control and exercise in obesity has to our knowledge, not been previously investigated and formed the basis of our study.

We hypothesized that obese Z rats possess altered adenosinergic modulation of ventilatory drive and peak oxygen consumption, compared with lean littermates. A parallel study design was used, with lean age-matched Z rats serving as controls.

Methods:

The studies were performed on 8 lean (Fa/?) and 8 obese (fa/fa) age-matched male Zucker (Z) rats.

The barometric technique with a 4L chamber was used for the measurement of breathing pattern and metabolic rates. The chamber was sealed and oscillations in pressure caused by breathing were recorded by a sensitive pressure transducer.

The exercise test to elicit peak aerobic exercise activity (VO2 peak) was performed in a metabolic treadmill. The treadmill slope was set at 20% for lean animals and 10% for obese animals and remained constant throughout the exercise test.

Oxygen consumption (VO2) and CO2 production (VCO2) were measured and calculated from inflow-outflow O2 and CO2, monitored by CO2 gas analyzer and O2 analyzer.

Animals underwent ventilatory testing at 8~9 weeks of age and underwent exercise test at 11~12 weeks of age. Animals were tested following an intraperitoneal (I.P.) injection of equal volumes (2 ml/kg) of saline (vehicle), 8-(p-sulphophenyl)-theophylline (7 mg/kg, 8-PST, an agent of peripheral adenosine antagonist), and aminophylline (15 mg/kg, AMPH, an agent of adenosine antagonist).

The planned comparisons with repeated measures analysis of variance under General Linear Model (GLM) in a one between (lean and obese) and two within (gases, drugs) design was conducted to analyze all parameters. In all cases, a difference at $P<0.05$ was considered statistically significant. All data presented in the text, Tables, and figures represent means ± SEM.

Results:

Male obese Z rats weights about 37% more than age-matched lean animals (290 ± 11 g vs. 187 ±4 g, $p<0.01$) during ventilatory test at 8~9 weeks of age and (512±10 vs. 314±3, $p<0.01$) during exercise test at 11~12 weeks of age.

During quiet breathing, AMPH significantly ($P<0.05$) increase resting VE in both lean and obese rats whereas 8-PST did not alter resting VE in both lean and obese Z rats (Fig1).

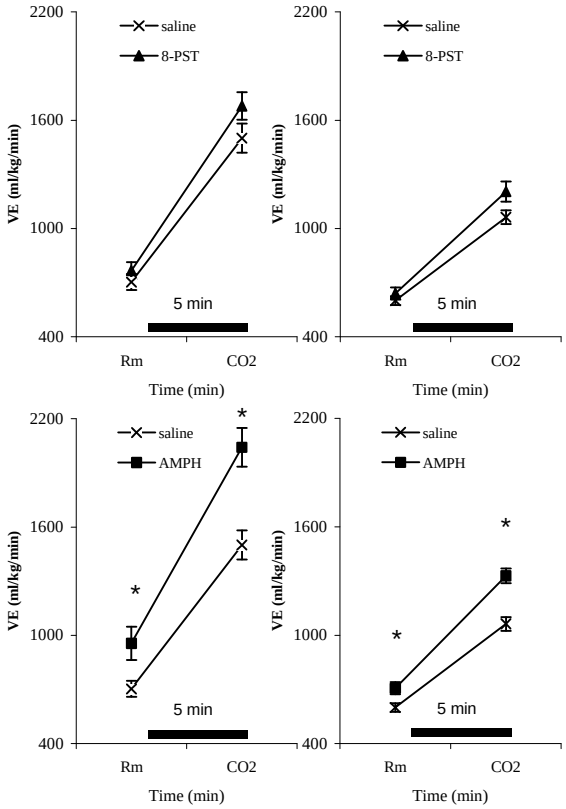

Figure 1

Effects of vehicle (cross mark), 8-PST (closed triangle, Upper panel), and AMPH (closed square, Lower panel) injection on ventilation (VE, ml/kg/min) during room air (Rm) and 5 min hypercapnic (8% CO2) exposure in lean (left panels) and obese (right panels) Zucker rats. *P < 0.05 a significant difference from the value of control at the same time point. Values represent mean ± SEM.

Ventilation (VE) in response to hypercapnic gas challenges was increased following the administration of AMPH compared to vehicle in both lean and obese Z rats. The administration of 8-PST had no significant effect on any respiratory parameter during CO2 exposure in both lean and obese Z rats (Fig 1).

In lean animals, VO2 peak was unaltered following 8-PST or AMPH compared with control values. In obese rats, AMPH administration significantly ($P<0.05$) increase VO2 peak whereas 8-PST did not alter VO2 peak. The average increase in VO2 peak for all eight obese animals following AMPH administration was about 18 % compared to control. The effects of 8-PST and AMPH administration on individual animals (Fig 2).

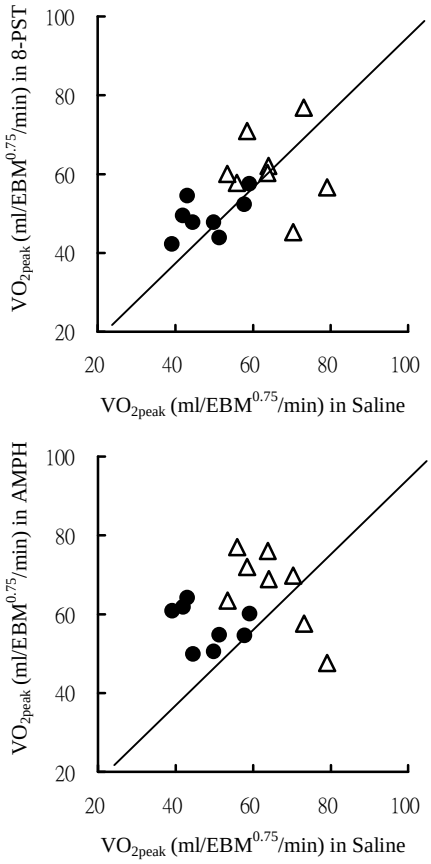

Figure 2
The effects of 8-PST (left panel) and AMPH (right panel) administration on relative peak oxygen consumption [VO2 peak (ml/kg0.75/min)] of individual lean (open triangles) and obese (closed circles) Zucker rats.

Discussion

Our major findings can be speculated as follows: 1) Endogenous adenosine depress ventilation during room air breathing and during hypercapnic challenges in both lean and obese Z. rats, and this ventilatory modulation is not mediated by peripheral adenosinergic mechanism; 2) endogenous adenosine do not modulate VO2 peak in lean Z rats, 3) VO2 peak is limited by altered adenosinergic mechanisms in obese Z rats, and the altered modulation of peak oxygen consumption is attributed to adenosine receptors located within the central nervous system. The findings support our hypothesis that obese Z rats possess altered adenosinergic modulation of peak oxygen consumption comparing with lean littermates.

Although the two adenosine antagonists, 8-PST and AMPH, are widely used and accepted to investigate the adenosinergic mechanism of respiratory control, both of them did produce a wide range of physiological responses (5). Therefore we have to add a note of caution prior to interpretation of our data, any effects noted here, cannot conclude any specific system which interacted by adenosinergic blockade. The goal of the present study, however, was to limited the scope of our study to differentiate the effects of endogenous adenosine exerting on ventilatory drive and maximal exercise capacity via acting on central or peripheral adenosine receptors between lean and obese Z rats. Clearly, additional experiments using a reductionist approach will be required in order to specifically identify the altered adenosinergic modulation of exercise.

The similar effects of AMPH administration on ventilation during room air breathing and during hypercapnic challenge were observed in both lean and obese Z rats, which potentially modulated by central, not by peripheral, adenosinergic system. AMPH administration (not 8-PST) led to an increase in VO2 peak in obese animals and lessened the difference between lean and obese animals. Thus, endogenous adenosine located at the central nervous system, which tonically

inhibits VO2 peak in obese animals, may partially account for their poor exercise capacity. Thus, we can speculate that the endogenous adenosine may exert significant physiological effect on exercise in obese adults.

Reference

1. Lee SD, Nakano H, Farkas GA. GABAergic inhibition of ventilation and peak oxygen consumption in obese Zucker rats. J Appl Physiol 90:1707-1713, 2001.
2. Lee SD, Nakano H, Gosselin LE, Krasney JA, Schlenker EH, Farkas GA. Endogenous opioids modulate ventilation and peak oxygen consumption in obese Zucker rats. Am J Resp Crit Care Med 162:1009-15. 2000.
3. Martin RJ, Harris RB, Jones DD. Evidence for a central mechanism of obesity in the Zucker fatty rat (fa/fa). Proceedings of the Society for Experimental Biology & Medicine. 183(1):1-10, 1986.
4. LaNoue KF, Martin LF. Abnormal A1 adenosine receptor function in genetic obesity. FASEB Journal. 8(1):72-80, 1994.
5. Bruns RF. Adenosine receptors: roles and pharmacology. Ann. NY Acad. Sci. 603: 211-225, 1990.

計畫成果自評

此研究內容與原計畫完全相符並達成預期目標也證實部分的假說。此研究成果頗具有高度的學術價值和應用價值。

我們的主要的研究成果在發現在基因胖鼠中改變的adenosine的機制位於中央神經系統部分導致在肥胖症中運動能力的不足。這些發現將延續且加強我們早先的發現在肥胖症中中央及周圍的神經調節的改變的確扮演重要的角色在肥胖的換氣反應不足和運動能力不足。可預計在不久的將來在學術期刊發表。

這研究實質的打開新的契機，去了解肥胖症中可能換氣異常和運動能力不足的病因，和其病生理的進程。除此之外，我們的資料將提供一個理論基礎來發展肥胖症運動能力不足可能的治療方法。