運動對學習記憶、焦慮、憂鬱及物質濫用之影響

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運動對腦功能的影響—運動對學習記憶、焦慮及物質濫用之影響
The impact of exercise on learning and memory, anxiety, depression and substance abuse

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一、中文摘要

物質濫用是台灣地區急速發展的國民身心健康議題。近年來的研究多指出運動合併抗憂鬱劑的使用可以回復輕、中度憂鬱或因慢性病引發憂鬱的症狀。而憂鬱症狀被認為是許多濫用藥物發展為依賴或上癮的危險因子。運動造成的長期效果及經濟特性提供了一個副作用少的非藥物治療焦慮、憂鬱、物質濫用的可能方式。我們在過去一年的研究以高架十字形迷津模型發現中長期及長期強迫運動效果可能改變該模型中的本能焦慮行為指標。心理運動刺激劑(例如近年來在臺灣地區氾濫使用的搖頭丸)的開始使用及戒除後復發皆受壓力這個因子的培基調控，長期強迫運動的效果之一是調整生物體對於壓力的易感性。我們在場地偏好物質依賴模型發現長期強迫運動能降低動物對心理運動刺激劑的強化效果。我們發現搖頭丸雖然可以刺激依核多巴胺的分泌，但是長期強迫運動似乎使依核產生神經適應性的改變效果。也就是說搖頭丸無法在長期強迫運動的動物依核中產生刺激多巴胺分泌的效果。

關鍵詞：運動、場地偏好、學習記憶、物質濫用、憂鬱、焦慮

Abstract

Substance abuse and dependence, seriously endangering both mental and physical health at gigantic cost, raise a major issue of concern in the local area. Psychomotor stimulants are, especially methamphetamine and MDMA (Ecstasy), substance abuse of choice in Taiwan. Accrued evidence revealed that exercise alone and/or in conjunction of anti-depressive drugs effectively alleviated the symptoms associated with a mild to moderate depression even well-controlled experiments still remain sparse. Anxiety and depression have been thought the risk factors for the development of substance abuse and dependence. Exercise, characterized by its long-lasting effects, inexpensive cost, and less side effects, deserves a full-scale understanding. We propose to examine the impact of long-term forced exercise program on altering the reinforcing effects in drug-induced place preference paradigm. We found that acute MDMA injection (intra-peritoneally) increased dopamine release in the nucleus accumbens. However, such drug treatment at the same dose did not alter the extracellular dopamine concentration in accumbal dialysate samples in long-term exercise animals.

Key words: exercise, substance abuse, learning and memory, depression, anxiety

二、Introduction

The growing size of senile population and competitive working conditions are thought to induce subjective stress, anxiety and depression, with a consequent decrea
se in the self-evaluated quality of life, circadian rhythm disturbances, attention-disrupted poor productivity and various drug abuses. Acute stress may suppress immune function, leading to an increased incidence of infections, and chronic stress may predispose to several ailments, including digestive disturbances, cardiovascular diseases and neoplasia. Thus, control of stress becomes an important issue in all modern societies. Although stress can not be avoided, its impact may be reduced by many recommended ways. Among them, physical activity/exercise can be one of the best alternatives, since exercise was not only thought to exert many positive effects on physical and psychological health with minor side effects but to possess a money-saving character.

Physical activity/exercise is associated with lower risks of cognitive impairment, and physical inactivity may be a risk factor for the Alzheimer’s disease (Friedland et al., 2001; Laurin et al., 2001). Physical activity and habitual exercise may have beneficial effects in both young and aged subjects. The exercise program appeared to have a greater effect on physiological functioning, concentration and short-term memory of younger subjects, while both young and old subjects achieved gains in physiological functioning, and psychological well-being (Emery, 1994). High intensity aerobic exercise has positive effects on well-being in an adolescent population (Norris et al., 1992). An individualized exercise program can improve a functional balance in people aged above 75 years and such improvement was maintained at least for one month (Wolf et al., 2001).

Many clinical studies reported that exercise may reduce age-related lean body mass loss and risk for several chronic diseases. Moderate muscle strength training demonstrated positive effects on clinical parameters in chronic heart failure patients (Radzewitz et al., 2002). Although inconclusive results have been reported for most treatment modalities, exercise appeared to decrease the myriad of physical symptoms associated with Fibromyalgia, a rheumatological disorder of unknown origin (Meyer and Lemley, 2000; Gowans et al., 2001). Graded exercise therapy have shown promising results in reversing the symptoms of chronic fatigue syndrome, characterized by severe disabling fatigue and a variety of musculoskeletal, cognitive and sleep disorders lasting at least six months (Youssefi and Linowski, 2002). To date, the general public is, perhaps, aware of the physical benefits of exercise, but less cognizant of the psychological merits of regular exercise. Psychological states such as mild-to-moderate anxiety, depression, and chronic diseases-associated dysthymia (a mild depression) have been found reduced by exercise and/or physical activity. Likewise, exercise has been claimed to elevate mood, increase intellectual functioning, and improve self-concept. Although people with depression tend to be less physically active than non-depressed individuals, increased aerobic exercise or strength training has been shown to reduce their depressive symptoms (Paluska and Schwenk, 2000). Anxiety symptoms and panic disorder also improve with regular exercise (Paluska and Schwenk, 2000). An exercise training program may be considered an alternative to antidepressants for tre
atment of depression in senile persons. Although antidepressants may facilitate a more rapid initial therapeutic response than exercise, exercise was equally effective in reducing depression among patients with major or depressive disorder after 16-wk of antidepressant treatment (Blumenthal et al., 1999). An appropriate application of exercise program was effective in relieving depression or anxiety in the long-term maintenance hemodialysis patients with common complaints of depression and anxiety (Suh et al., 2002). Mild to moderate aerobic exercise may be of therapeutic value to breast cancer survivors with respect to depressive and anxiety symptoms (Segar et al., 1998). Healthy subjects showed increased physiological and psychological indices of relaxation after underwater exercise (Oda et al., 1999). Overall results revealed that exercise-induced increases in aerobic fitness have beneficial short-term and long-term effects on psychological outcomes (DiLorenzo et al., 1999). Exercise was associated with decreases in total mood disturbance, as well as increases in vigor in physically active postpartum women (Koltyn and Schultes, 1997).

However, claims for the psychological benefits of physical exercise appear to precede solid evidence. The emotional effects of acute exercise still remain controversial. Some claimed that acute exercise, a dynamic version of Takwondo, induced positive mood state changes and long-term exercise, extensive Takwondo skill, did not necessarily elicit beneficial changes in affect (Toskovic, 2001), while others emphasized the paucity of effects following acute exercise. Long-term exercise exerts the antidepressant and anxiolytic effects and mitigates the harmful consequences of stress mostly limited in subclinical studies. Studies attempted to link exercise habits to protection from harmful effects of stress on mental health, but causality remains unclear. Moreover, conflicting data on physical activity modalities hinder any general conclusion. For example, a buffering effect for leisure physical activity was suggested against physical symptoms and anxiety associated with minor stress, while no moderating effect for aerobic fitness was found in this regard (Carmack et al., 1999). Physical activity of long duration amongst men conferred protection against common mood and anxiety states, while no such protection for women (Bhui and Fletcher, 2000). Furthermore, exercise, as performed strenuously, could be associated with increased production of reactive oxygen species, consuming endogenous antioxidants and eventually damaging biological molecules and cellular components. Likewise, excessive physical activity is thought to result in overtraining and generate psychological symptoms that mimic depression. Thus, well controlled studies are needed to elucidate the mental benefits of exercise in differing populations and to address the biological mechanisms underlying the benefits of exercise on mental health.

As for animal studies, sparse paradigm has been attempted to examine the modulating effects of exercise/physical activity on reversing behavioral, neurochemical, or neuroendocrine parameters associated with depression and/or anxiety. Dishman (1997) reported that voluntary (chronic activitywhele running) and forced exercise (treadmill...
exercise training) exerted anxiolytic and antidepressant effects via reversing behavioral, neurochemical versus neuroendocrine parameters, respectively. The voluntary wheel running increases neurogenesis and long-term potentiation in the dentate gyrus, and enhances spatial learning performance (Fordyce et al., 1993; van Praag et al., 1999a; van Praag et al., 1999b), while stress caused atrophy of dendrites in the CA3 region and suppresses the neurogenesis of dentate gyrus neurons (McEwen, 1999). However, the results of most these studies compromise with the methodological flaws, such as the loosely-controlled intensity of exercise and genetic backgrounds, dissimilar exercise protocols as well as the incompatible sampling timing. In an attempt to avoid these weaknesses, we employed consistently the same paradigms (CPP and EPM), forced exercise protocols, sampling timing in mouse models with similar genetic backgrounds.

Specific Aims
We decided to examine the modulating effects of long-term forced exercise on the reinforcing/euphoric effects of MDMA. We employed microdialysis approach to examine the dopamine-releasing effects of MDMA in both long-term exercise and control animals.

Materials and methods

Animal models: Since one report documented that there were sexual differences in exercise-generated benefits, only male C57 BL/6 mice (3 months old) were used as the animal model in the experiments. Mice were group-housed (5 per cage) with free access to mouse chow and tap water in a humidity- and temperature-controlled colony room and laboratory maintained on a 12 h light/dark cycle unless mentioned otherwise. All experimental procedures and use of animals have been approved by the local committee at National Cheng Kung University College of Medicine (see attached).

Exercise protocols: Under the forced exercise protocol, following one-week familiarization, mice in the medium- and long-term exercise groups run on a treadmill at the speed of 12 m/min for 60 min/day, 5 days/wk, 1 and 12 weeks in total, respectively. In contrast, the sedentary groups experienced one-week familiarization, then, were placed on the yoked treadmill for 10 min each day except any exercise training.

In vivo microdialysis:
Cannula implantation: An incision was made in the scalp and the temporalis muscle will be retracted to expose a section of the skull. Two holes approximately 2 mm in diameter will be drilled in the skull, and guide cannulae which will be implanted bilaterally in the nucleus accumbens (NAc).

Microdialysis procedures: Using a CMA/102 microinfusion pump and FEP Teflon tubing, artificial cerebrospinal fluid was perfused through an analytical probe for 20 min prior to its insertion into the guide cannula. Following insertion, the flow rate was reduced to 1.0 μl/min. Samples were collected at 20-min intervals to measure basal dopamine levels. High-performance liquid chromatography (HPLC) was used to quantify levels of dopamine in the dialysates samples.
**Conditioned Place Preference:** Mouse Place Preference Instrument ENV-3013 and Software (Georgia, Vermont, Med Associate, USA) were used. Mice were first translocated from their home cages to the instrument for a 10-min adaptation to assure the unbiased design. Mice, then, were injected, intraperitoneally, with MDMA (Ecstasy at 1.67 mg/kg) and restrained in one compartment chamber for 30 minutes and back to their home cages. Vehicle were given 8 hours later in the same day and animals were restricted in the other compartment chamber for 30 minutes. The regimen were repeated for totally 3 times. On day 4, mice were translocated into the neutral chamber and started immediately (program-controlled) a 15-min test session with free access to all compartment chambers. The total time spent and locomotor activity in every chamber (methamphetamine-associated, vehicle-associated, neutral) were automatically recorded.

**Statistical Analysis:**

Data were expressed as mean ± SEM. The results were analyzed by unpaired Student’s t test, ANOVA, or nonparametric analysis whenever applicable. The P values less than 0.05 were considered statistically significant.

### Result and discussion

1. Long-term forced exercise and MDMA-induced place preference—We found that long-term forced exercise “dose-dependently” decreased the MDMA-induced place preference. Four weeks of exercise did not alter the MDMA-induced place preference. In contrast, we observed that 8- and 12-wk exercise effectively decreased the MDMA-induced place preference. (Figure 1).

2. Long-term forced exercise and the MDMA-induced dopamine release in the nucleus accumbens—We found that long exercise did not alter the baseline levels of dopamine in the nucleus accumbens. Although MDMA effectively enhanced the accumbal dopamine release in control mice, MDMA did not produce such elevation in extracellular dopamine in the exercise animals (Figure 2).

### Self evaluation

Our progress is promising at this stage. We not only established the long-term exercise protocol, we also found that for the first time that long-term exercise may reduce the MDMA-associated behavior-reinforcing effects and the dopamine-releasing effects in the nucleus accumbens. We expect to examine the modulating effectsof long-term exercise on the other abused drug of choice to reinforce the rationale that long-term exercise may reduce the naïve anxiety levels and mitigate the attractiveness of psychomotor stimulants.

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