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運動對學習記憶、焦慮、憂鬱及物質濫用之影響

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The impact of exercise on learning and memory, anxiety, depression and substance abuse

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 (Ecstacy), substance abuse of choices 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 depressive symptoms. 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 found that mid- and long-term compulsive exercise effectively decreased the anxiety responses in elevated plus maze paradigm. Moreover, pre-exposure to long-term exercise mitigated the reward/hedonic value of 3,4-methylenedioxymethamphetamine (MDMA) in the MDMA-induced conditioned place preference (CPP) paradigm. We found that the long-term forced exercise program that we used abolished the MDMA-stimulated dopamine release in nucleus accumbens. Although the same exercise program did not alter the methamphetamine (MA)-induced CPP, such program effectively mitigated MA-induced serotonergic deficits in striatum. We hereby conclude that long-term exercise is beneficial in 1) curbing the hedonic value of MDMA, thus the development of MDMA dependence and abuse and 2) MA-induced central serotonergic neurotoxicity.

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

The growing size of senile populations and competitive working conditions are thought to induce subjective stress, anxiety and depression, with a consequent decrease 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 Linkowski, 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 as 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 treatment 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 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

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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 attempt 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 paradigms have been attempted to examine the modulating effects of exercise/physical activity on 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 (conditioned place preference for the hedonic/reward value of abused drugs, elevated plus maze for induced stress response and novelty environment-linked locomotor activity and exploration for naïve stress level), forced exercise (treadmill running) protocols, standard sampling timing in mouse models with similar genetic backgrounds.

Specific Aims
We decided to examine the modulating effects of long-term compulsive exercise on the euphoric/reward effects of MDMA and methamphetamine. We employed microdialysis approach to examine the dopamine-releasing effects of MDMA in both long-term exercise and control animals. We determine the effects of compulsive exercise exposure on modulating methamphetamine-induced central monoamine neurotoxicity.

Materials and methods
Animal models: Since one report documented that there were sexual differences in exercise-generated benefits, only male C57BL/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 temporal 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 refrained 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.

**Assay for monoamine neurotransmitter and their metabolite levels by HPLC**

A 14-day recovery period awaited following MA dosing regimen. Mice were killed by rapid decapitation and a portion of striatum, prefrontal cortex, hippocampus, amygdala, nucleus accumbens from two hemispheres were dissected. Brain tissues were stored in liquid nitrogen until assayed by HPLC with an LC-4C amperometric detector (BAS, West Lafayette, IN) for measuring DA, DOPAC, 5-HT, and 5-HIAA levels. Striatal tissues were homogenized in 0.4N perchloric acid and centrifuged at 16,000 × g for 20 min at 4°C. The supernatant was filtered and delivered through a high-pressure valve fitted with a 20-µl loop onto a Phase-II ODS column (3 µm, 3.2 mm i.d. x 10 cm), and oxidized with a +0.72-V potential between the glassy carbon electrode and the Ag/AgCl reference electrode. The mobile phase consisted of 0.1 M sodium phosphate dibasic, 0.1 M citric acid, 5 mg EDTA, and 7 % methanol delivered at a 0.6-ml/min flow rate.

**Statistical Analysis:** Data were expressed as mean + SEM if not mentioned otherwise. 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 compulsive exercise did not alter the MDMA-induced conditioned place preference (CPP). Eight weeks of exercise seemed to reduce the MDMA-induced CPP. Surprisingly, we observed that 12-wk compulsive exercise effectively decreased the MDMA-induced CPP (Figure 1). Nonetheless, compulsive exercise did not appear to affect the methamphetamine-induced CPP regardless of the exercise duration that we used at...
similar regimen.

2. Long-term forced exercise and the MDMA-induced dopamine release in the nucleus accumbens— We found that 12-wk 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).

3. Pre-exposure of long-term (12 weeks) compulsive exercise mitigate the methamphetamine-induced serotonergic deficits in striatum and nucleus accumbens (Figure 3).

四 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 rein forcing effects and the dopamine-releasing effects in the nucleus accumbens. We expect to examine the modulating effects of 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.

五 References


Figure 3-1. 8-wk exercise on methamphetamine-induced 5-HT depletion in striatum (N = 5) CSS: sedentary control mice receiving saline. CMS: sedentary control mice receiving methamphetamine. ESS: 12-wk exercised mice receiving saline. EMS: 12-wk exercised mice receiving methamphetamine.

Figure 3-2. 12-wk exercise on methamphetamine-induced 5-HT depletion in striatum (N = 8)

Figure 3-3. 8-wk exercise on methamphetamine-induced 5-HIAA depletion in striatum (N = 5) CSS: sedentary control mice receiving saline. CMS: sedentary control mice receiving methamphetamine. ESS: 12-wk exercised mice receiving saline. EMS: 12-wk exercised mice receiving methamphetamine.

Figure 3-4. 12-wk exercise on methamphetamine-induced 5-HIAA depletion in striatum