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DEPARTMENT OF PHYSICAL EDUCATION AND SPORT SCIENCE

EFFECTS OF ACUTE EXERCISE ON SMOKING BEHAVIOUR AND HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN SMOKERS

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in “Exercise and Health” at the Department of Physical Education and Sport Science, University of Thessaly

JANUARY 2020

FUNDING

This study was co-financed by the European Union [European Social Fund (ESF)] and Greek national funds through the Operational Program 'Education and Lifelong Learning' of the National Strategic Reference Framework Research Funding Program: THALES. Investing in knowledge society through the ESF.

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ΕΥΧΑΡΙΣΤΙΕΣ

Θα ήθελα να ευχαριστήσω θερμά τον καθηγητή κ. Αθανάσιο Τζιαμούρτα που με εμπιστεύτηκε για την υλοποίηση της παρούσης μεταπτυχιακής διατριβής, καθώς και την πολύτιμη υποστήριξη, βοήθεια και καθοδήγησή του καθ' όλη τη διάρκεια της συνεργασίας μας. Επιπλέον, ευχαριστώ την κ. Γεωργακούλη Καλλιόπη, πολύτιμη συνεργάτιδά μου στην εκπόνηση της παρούσης εργασίας, για την άψογη συνεργασία, τη βοήθεια και τις συμβουλές της. Τις ευχαριστίες μου απευθύνω επίσης και στα υπόλοιπα μέλη της τριμελούς επιτροπής καθηγητών κ.κ. Φατούρο Ιωάννη και Χατζηγεωργιάδη Αντώνιο για τις σημαντικές επισημάνσεις τους, που συντέλεσαν στη βελτίωση της διατριβής. Τέλος, για άλλη μια φορά ευχαριστώ την οικογένειά μου, η οποία πάντα με στηρίζει, και ιδιαίτερα τον πατέρα μου, που δεν βρίσκεται πια κοντά μας.

Effects of acute exercise on smoking behaviour and hypothalamic-pituitary-adrenal axis in smokers
(Under the Supervision of Professor Athanasios Z. Jamurtas)

ABSTRACT

***Background*:** Exercise and physical activity have been suggested as a useful method of attempting to quit smoking, as an adjunct to existing treatments. In this way exercise can contribute to both smoking cessation and avoiding the adverse effects of smokingon human health. ***Purpose*:** The purpose of this study was to determine the effect of acute aerobic exercise on smoking urge, as well as on some biomarkers such as the hypothalamic-pituitary-adrenal axis (HPA) hormones. ***Methods*:** Twenty five smokers with non-declared pathology (age: 33±1.4 years) underwent three trials [moderate intensity (MI) and high intensity (HI) exercise, control (C)] after an overnight fast and smoking abstinence, separated by at least six days. MI involved cycling at 50-60% of Heart Rate Reserve (HRR) for 30 min, HI at 65-75% HRR for 30 min, while in C participants rested quietly for 30 min. Blood samples were taken before and immediately after each trial and β-endorphin (β-E), adrenocorticotropic hormone (ACTH), cortisol and catecholamines (epinephrine, norepinephrine) were measured. ***Results*:** ACTH, catecholamines, cortisol and β-E levels increased following exercise compared to resting, with greater increases being noted following HI. Smoking urge did not change after any trial; however, time till first cigarette increased significantly following HI compared to C (20.1±5.1 min vs 11.3±5.2 min). ***Conclusion*:** Acute aerobic exercise of moderate and high intensity increases β-endorphin, ACTH, cortisol and catecholamine levels with greater increases observed high intensity exercise. High intensity aerobic exercise could be potentially used as an adjunct in smoking cessation.

Key Words: *hormones, exercise; smoking; nicotine; addiction*

Επιδράσεις της οξείας άσκησης στην καπνιστική συμπεριφορά και την ενεργοποίηση του άξονα υποθαλάμου-υπόφυσης-επινεφριδίων σε καπνιστές
(υπό την καθοδήγηση του Καθηγητή Αθανασίου Τζιαμούρτα)

ΠΕΡΙΛΗΨΗ

Η άσκηση και η φυσική δραστηριότητα έχουν προταθεί ως χρήσιμη μέθοδος στην προσπάθεια διακοπής του καπνίσματος, επικουρικά στις ήδη υπάρχουσες θεραπείες. Με τον τρόπο αυτό μπορεί να συνεισφέρει τόσο στη διακοπή του καπνίσματος αλλά και στην αποφυγή των δυσμενών συνεπειών του στην ανθρώπινη υγεία.

Σκοπός: Σκοπός της παρούσας μελέτης ήταν η διερεύνηση της επίδρασης της οξείας αερόβιας άσκησης στην ανάγκη για κάπνισμα, καθώς και σε ορισμένους βιοδείκτες όπως οι ορμόνες του υποθάλαμο-υπόφυσιο-επινεφριδιακού άξονα. ***Μέθοδοι:*** Εικοσιπέντε καπνιστές με μη δηλωμένη παθολογία (μέση ηλικία: 33±1.4 έτη) πραγματοποίησαν 3 διαφορετικές δοκιμασίες (άσκηση μέτριας έντασης, άσκηση υψηλής έντασης και σε ηρεμία), μετά από ολονύκτια νηστεία και αποχή από το κάπνισμα, με χρονική διαφορά έξι ημερών μεταξύ των δοκιμασιών. Η δοκιμασία μέτριας έντασης περιελάμβανε ποδηλασία στο 50-60% της μέγιστης καρδιακής εφεδρείας, η δοκιμασία άσκησης υψηλής έντασης 65-75% ενώ η δοκιμασία ελέγχου ανάπαυση για 30 λεπτά. Αιμοληψίες πραγματοποιήθηκαν πριν από κάθε δοκιμασία και αμέσως μετά την ολοκλήρωσή της, και μετρήθηκαν τα επίπεδα β-ενδορφίνης, φλοιοεπινεφριδιοτρόπου ορμόνης (ACTH), κορτιζόλης και κατεχολαμινών (επινεφρίνη, νορεπινεφρίνη, ντοπαμίνη). ***Αποτελέσματα:*** Τα επίπεδα β-ενδορφίνης, ACTH, κορτιζόλης και κατεχολαμινών αυξήθηκαν μετά την άσκηση συγκριτικά με την ηρεμία, με τις μεγαλύτερες αυξήσεις να σημειώνονται μετά από άσκηση υψηλής έντασης. Η επιθυμία καπνίσματος δεν μεταβλήθηκε μετά από καμία δοκιμασία, όμως ο χρόνος μέχρι το επόμενο τσιγάρο αυξήθηκε σημαντικά μετά από άσκηση υψηλής έντασης συγκριτικά με τη συνθήκη ελέγχου (20.1±5.1 λεπτά έναντι 11.3±5.2 λεπτά). ***Συμπεράσματα:*** Η αερόβια άσκηση

υψηλής και μέτριας έντασης αυξάνει οξέως τα επίπεδα β-ενδορφίνης, ACTH, κορτιζόλης και κατεχολαμινών με τις μεγαλύτερες αυξήσεις να παρατηρούνται σε υψηλής έντασης άσκηση. Η υψηλής έντασης αερόβια άσκηση μπορεί πιθανά να συνεισφέρει στη διακοπή του καπνίσματος.

Λέξεις κλειδιά: *ορμόνες, άσκηση, κάπνισμα, νικοτίνη, εθισμός.*

ABRREVIATION LIST

CDC: Center for Disease Control and Prevention

ACTH: Adrenocorticotropic hormone

β-E: beta-endorphin/ β-endorphin

HPA: Hypothalamo-Pituitary-Adrenal

MET: Metabolic equivalent of task

ACSM: American College of Sports Medicine

HRR: Heart Rate Reserve

HR: Heart Rate

LTPA: Leisure-time physical activity

PA: Physical activity

CVD: Cardiovascular disease

CVRF: Cardiovascular risk factor

CHD: Coronary heart disease

LDL-c: Low density lipoprotein cholesterol

HDL-c: High density lipoprotein cholesterol

TG: Triglycerides

T2DM: Type 2 Diabetes Mellitus

RR: Relative risk

RCT: Randomized controlled trial

WHO: World Health Organization

COPD: Chronic Obstructive Pulmonary Disease

BMD: Bone mineral density

CA: Cancer

NHIS: National Health Interview Survey

POMC: Proopiomelanocortin

CRH: Corticotrophin releasing hormone

GC: Glucocorticoids

CBT: Cognitive-behavioral treatment

LI: Light intensity

MI: Moderate intensity

HI: High intensity

EOT: End of treatment

EOFU: End of follow-up

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1. INTRODUCTION

Smoking is the most common addictive habit and a remarkable cause of morbidity and mortality. Recent epidemiological data from 2015 report that despite reductions compared to the previous decade, still one in five adults over 15 years make use of cigarette (Onor et al., 2017). According to the Center for Disease Control and Prevention (CDC) ("Quitting smoking among adults--United States, 2001-2010," 2011) an important proportion (almost 70%) of smokers is willing to quit, the number of successors is though substantially lower (6.2%). Tobacco smoking is a major predisposing factor for cardiovascular (Benowitz & Burbank, 2016; Onor et al., 2017; Shah & Cole, 2010) and pulmonary disease (Buist, Vollmer, & McBurnie, 2008; Feldman & Anderson, 2013). In addition, smoking has a well-established causal relationship with cancer and predominantly the pulmonary type (Walser et al., 2008).

Exercise and physical activity have been proposed as an adjunct strategy in smoking cessation efforts and various mechanisms are considered to be involved in this process (Roberts, Maddison, Simpson, Bullen, & Prapavessis, 2012). Thus, apart from the abundant beneficial effects in human health and mostly cardiovascular disease (Lin et al., 2015; Ozemek et al., 2018; Sui, Sarzynski, Lee, & Kokkinos, 2017) accumulating research associates exercise with smoking cessation (Klinsophon, Thaveeratitham, Sitthipornvorakul, & Janwantanakul, 2017; M. H. Ussher, Taylor, & Faulkner, 2014). Recently, a biological background of the influence of exercise in smoking urge has been proposed and the role of beta-endorphin (β-E) and the hypothalamic-pituitary-adrenal (HPA) axis has been under investigation (Manthou et al., 2016). In this study we aimed to assess the effects of acute exercise of different intensities on smoking urge and specific biomarkers i.e. β-E, ACTH, cortisol and catecholamines.

1.1. RESEARCH SIGNIFICANCE

Exercise could be an effective treatment for smokers. However, more research needs to be done in order to understand the possible mechanisms involved in the reduction or stopping smoking. A possible physiological mechanism that links exercise and smoking habit and hormone secretion has been proposed, indicating that exercise could be used as a significant stressor for hormone secretion.

The purpose of this study was to investigate the effect of acute high and moderate intensity exercise on peptides of the HPA axis and smoking habits. It is an attempt to evaluate how exercise influences physiological changes that could contribute to smoking reduction.

1.2. RESEARCH HYPOTHESES

i) A bout of acute exercise of moderate intensity will increase blood β-E levels in smokers.

i) A bout of acute exercise of moderate intensity will reduce smoking urge in smokers.

ii) A bout of acute exercise of high intensity will increase blood β-E levels in smokers.

iii) A bout of acute exercise of high intensity will influence the levels of peptides of the HPA axis in smokers

1.3. STATISTICAL HYPOTHESES

Null hypotheses

i) Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences between rest and exercise (pre- and post- exercise trial) in β-E levels in smokers.

Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences between rest and exercise (pre- and post- exercise trial) in smoke urge smokers.

Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences between rest and exercise (pre- and post- exercise trial) in the levels of peptides of the HPA axis in smokers.

Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences in smoking urge at rest, and following moderate and high intense exercise in smokers.

Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences in β-E levels urge at rest, and following moderate and high intense exercise in smokers.

Null hypothesis ($\mu 1 = \mu 2$): There will be no statistical significant differences in the levels of peptides of the HPA axis at rest, and following moderate and high intense exercise in smokers.

Alternative hypotheses

i) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences between rest and exercise (pre- and post- exercise trial) in β-E levels in smokers.

i) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences between rest and exercise (pre- and post- exercise trial) in smoke urge smokers.

ii) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences between rest and exercise (pre- and post- exercise trial) in the levels of peptides of the HPA axis in smokers.

iii) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences in smoking urge at rest, and following moderate and high intense exercise in smokers.

iv) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences in β-endorphin and smoking urge at rest, and following moderate and high intense exercise in smokers.

v) Alternative hypothesis ($\mu 1 \neq \mu 2$): There will be statistical significant differences in the levels of peptides of the HPA axis at rest, and following moderate and high intense exercise in smokers.

1.4. RESEARCH LIMITATIONS

A limitation of the study is the small number of subjects due to practical difficulties in finding individuals that fulfill the requirements. Smoking often associates with co-morbidities (e.g. cardiovascular, respiratory disorders) meaning that in many cases high intensity physical exercise is contraindicated. Furthermore, the absence of control subject group sets limitations to our study. Finally, many smokers do not realize that they are facing an addictive and harmful problem.

2. LITERATURE REVIEW

2.1. DEFINITIONS RELATED TO EXERCISE AND PHYSICAL ACTIVITY

Exercise and physical activity are two quite common terms and are widely used by the largest portion of population with no adherence to their scientific or formal definitions. Furthermore they are comprised of different components which occasionally replace them in everyday life. However, the comprehension and accurate interpretation of medical or scientific studies regarding these concepts requires knowledge on their precise definitions as they have been established by international guidelines. The most recent version of the Physical Activity Guidelines Advisory Committee Scientific Report (Piercy et al., 2018) suggests the following definitions:

2.1.1. GENERAL DEFINITIONS

i) **Physical activity**: Every bodily movement produced by skeletal muscles that results in energy expenditure. The term does not require or imply any specific aspect or quality of movement and encompasses all types, intensities, and modes.

ii) **Exercise**: Physical activity that is planned, structured, repetitive, and designed to improve or maintain physical fitness, physical performance, or health. Exercise encompasses all intensities.

iii) **Non-exercise physical activity**: All physical activity that is not exercise.

iv) **Sedentary behavior:** Any waking behavior characterized by an energy expenditure of 1.5 or fewer METs, while sitting, reclining or lying.

2.1.2. TYPES OF PHYSICAL ACTIVITY

i) **Aerobic physical activity**: Forms of activity that are intense enough and performed long enough to maintain or improve an individual's cardiorespiratory fitness. Aerobic activities commonly require the use of large muscle groups. Examples of aerobic activities include walking, basketball, soccer, wheelchair rolling, or dancing.

ii) **Anaerobic physical activity:** High-intensity activity that exceeds the capacity of the cardiovascular system to provide oxygen to muscle cells for the usual oxygen-consuming metabolic pathways. Anaerobic activity can be maintained for only a short period of time, about 2 to 3 minutes. Sprinting and power lifting are examples of anaerobic physical activity.

iii) **Resistance training.** A method of muscle-strengthening activity or conditioning that involves the progressive use of resistance to increase one's ability to exert or resist force.

- **Isometric resistance exercise:** A type of muscle contraction during which the muscle generates force without lengthening and movement of the object.
- **Dynamic resistance exercise:** A type of contraction during which the muscle generates force by changing length to move an object.

2.1.3. VARIATIONS OF PHYSICAL ACTIVITY

Activities of daily living: Activities required for everyday living, including eating, bathing, toileting, dressing, getting into or out of a bed or chair, and basic mobility.

Instrumental activities of daily living: Activities related to independent living, including preparing meals, managing money, shopping for groceries or personal items, and performing housework.

Household physical activity: Activity done in or around the home, such as cooking, cleaning, home repair or gardening.

Leisure-time physical activity: Discretionary activity performed when one is not working, transporting oneself to a different location, or doing household chores. Sports or exercise, going for a walk, and playing games (football, basketball), are examples of leisure-time physical activity.

Occupational physical activity: Activity performed at work, such as stocking shelves in a store, delivering packages in an office, preparing or serving food in restaurant, or carrying tools in a garage are examples of occupational physical activity.

Transportation physical activity: Activity performed to get from one place to another, such as walking to and from work, school, or shopping.

2.1.4. EXERCISE INTENSITY

Absolute intensity: The rate of energy expenditure required to perform any given physical activity. It can be measured in metabolic equivalents, kilocalories, joules, or milliliters of oxygen consumption.

Relative intensity: Relative intensity refers to the ease or difficulty with which an individual performs any given physical activity. It has a physiologic basis and can be described using physiologic parameters, such as percent of aerobic capacity (VO_{2max}) or percent of maximal heart rate. Relative intensity can also be estimated by self-report of level of perceived exertion during an activity.

Commonly used classification of absolute exercise intensities:

Sedentary activity: Activity requiring 1.0 to 1.5 METs, such as sitting and reading or watching television, or standing quietly.

Light intensity: Activity requiring 1.6 to less than 3.0 METs, such as walking at a slow pace (2 mph or less) or cooking.

Moderate intensity: Activity requiring 3.0 to less than 6.0 METs, such as walking briskly (3 to 4 mph), mopping or vacuuming, or raking a yard.

Vigorous or high intensity: Activity requiring 6.0 or greater METs, such as walking very fast (4.5 to 5 mph), running, mowing grass with a hand-push mower, or participating in an aerobics class.

RELATIVE INTENSITY

According to the American College of Sports Medicine (ACSM) relative exercise intensity is stratified in 5 levels: Very light, Light, Moderate, Vigorous, Near-Maximal. Intensity thresholds vary with regard to the objective intensity marker (%HRR, $\%VO_2R$, $\%HR_{max}$, $\%VO_{2max}$) which is being used (Garber et al., 2011). Values of each level are shown in Table 1. Still, despite these proposed definitions there is a considerable variety in upper and lower limits of each level across studies.

Table 1. American College of Sports Medicine classification for relative exercise intensity.

Intensity	%HRR or $\%VO_2R$	$\%HR_{max}$	$\%VO_{2max}$
Very light	<30	<57	<37
Light	30-39	57-63	37-45
Moderate	40-59	64-76	46-63

Vigorous	60-89	77-95	64-90
Near-maximal	≥90	±96	≥91

2.2. EXERCISE SYSTEMATIC EFFECTS

Exercise confers plenty of benefits in physical and mental health and these associations are well-established. Current guidelines, as well as prior guideline versions, strictly contraindicate sedentary lifestyle and firmly suggest that exercise should be adopted in everyday life (Piercy et al., 2018). In brief, it is recommended that adults achieve a target of 150-300 minutes of moderate intensity aerobic exercise per week or 75-150 minutes of vigorous intensity per week as an alternative. Combining moderate intensity and vigorous aerobic activity to reach the above targets is also recommended. Muscle strengthening activities are encouraged to be performed 2 times a week. Modifications and adjustments are acceptable and recommended according to individual characteristics and capabilities.

2.2.1. CARDIORESPIRATORY SYSTEM AND DISEASE

The alterations of exercise in cardiovascular health are the most popular and probably the landmark among the variety of its beneficial effects, given the huge burden of cardiovascular disease in health and economy ("Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016," 2017). Cardiovascular disease is the most common cause of mortality in the United States according to recent evidence, accounting for more than 900,000 deaths in 2016. The optimal way to restrain this substantial factor of morbidity and mortality is to intervene

in the so called modifiable risk factors related to cardiovascular disease (hypertension, diabetes, dyslipidemia, obesity, smoking etc). Another efficient intervention which can act synergistically with medication is promoting and adopting a new, exercise-including lifestyle. There is accumulating literature supporting the beneficial effects of exercise in cardiovascular health (Maessen et al., 2016; Ozemek et al., 2018; Sui et al., 2017). Maessen et al. implemented a study, enrolling a large population, in order to determine the relationship between different doses of life-long exercise, including control group, with cardiovascular disease (CVD) and risk factors (CVRF) incidence. After a mean follow-up period of 32 years, all participants who reported life-long exercise participation had significantly lower prevalence of CVD and CVRF compared to those reporting no exercise. Interestingly, the highest benefit was observed in the subgroup reporting an exercise pattern similar to current recommendations. However, additional levels of exercise failed to provide an extra benefit. Conclusively, a reverse J-shaped association between exercise levels and cardiovascular morbidity was demonstrated by this study. Older evidence had proposed exercise as an independent predictor of coronary heart disease (CHD) (Morris et al., 1973; Sesso, Paffenbarger, & Lee, 2000). A large meta-analysis (Sattelmair et al., 2011) corroborated this hypothesis associating leisure time physical activity (LTPA) with lower risk for coronary heart disease (CHD). Individuals who reach the equivalent of 150min/w of moderate LTPA, the first target recommended by guidelines, have an estimated 14% risk reduction for CHD compared to non-exercisers. In addition, 300min/w of moderate LTPA conferred a further benefit of 6% risk reduction while LTPA levels below recommendations offered a significant risk reduction compared to exercise absence. Multiple pathophysiological mechanisms and pathways are considered to contribute to these results including regulation of endothelial dysfunction, vascular formation and modifications and platelet function alterations (Winzer,

Woitek, & Linke, 2018). However, a deeper, more detailed reference would outdo this study's aims.

In contrast to CHD, evidence from existing studies regarding physical activity and stroke, as a single outcome, is not that rich and explicit. Also, vigorous exercise associated with decreases in stroke incidence risk but results regarding physical activity as an independent protective factor were not consistent. Instead non-participation in exercise is associated with significantly elevated risk for stroke occurrence. Despite that, PA engagement showed a trend to reduce the risk for stroke only when performed 4 times/w or more frequently. A recent study in Korea demonstrated that moderate to vigorous PA is associated with lower risk for stroke and ischemic stroke with no differentiation among frequency subgroups (1-2, 3-4, ≥5 times/wk) (Jeong et al., 2017). The aforementioned evidence is indicative of the efficiency of exercise and PA in primary prevention of cardiovascular disease.

Cardiorespiratory fitness (CRF) is currently an important vital sign, providing valuable insight into cardiovascular and respiratory capacity (Ross et al., 2016; Sui et al., 2017) and exercise is a major contributor to higher CRF levels (Lin et al., 2015). Despite the fact that CRF has been considered an independent prognostic marker of CVD for long (Fletcher et al., 1996), strong recommendations for its integration in daily practice for cardiovascular risk stratification have been recently available (Ross et al., 2016). This is reflected in different studies, showing that CRF is associated with reduced risk for CVD events (Gander et al., 2015; Kodama et al., 2007; P. F. Kokkinos et al., 2017; Radford et al., 2018), incident heart failure (Kondamudi, Haykowsky, Forman, Berry, & Pandey, 2017; Myers et al., 2017), sudden cardiac death (Jimenez-Pavon et al., 2016) and all-cause mortality (Davidson, Vainshelboim, Kokkinos, Myers, & Ross, 2018; Kodama et al., 2007; Ross et al., 2016).

CRF is similarly associated with major CVD risk factors as hypertension and plasma lipoproteins. The inverse association between CRF and therefore exercise and incident

hypertension is well-established by rich literature (Barlow et al., 2006; Chase, Sui, Lee, & Blair, 2009; P. Kokkinos, 2014; Peter Kokkinos & Myers, 2010), with estimations for up to 19% (Barlow et al., 2006) risk reduction. These benefits are not applied only on normotensive individuals, as aerobic exercise in people with stage 1-2 hypertension can significantly lower blood pressure levels in comparison with non-exercisers (P. Kokkinos, 2014; P. F. Kokkinos et al., 1995). Moreover, an inverse association between higher levels of CRF and progression from prehypertension was reported, a well-known precursor for hypertension, into hypertension. However, these effects were met only in exercise capacity exceeding 8.5 METs. Those who carry out exercise training and have improved CRF, seem to have a better lipid profile, mainly attributed to HDL-c and triglycerides (TG) (Lin et al., 2015; Sui et al., 2017), while evidence regarding LDL-c as a unit are not clear (Lin et al., 2015). There seems to be a consistency between baseline CRF-lipids and longitudinal CRF levels-lipids associations (Breneman et al., 2016). Still, a plethora of other observational studies demonstrate controversial results and more research are needed to reach more accurate conclusions.

The role of exercise in reducing cardiovascular morbidity and mortality is not restricted in primary prevention as individuals who have experienced a CV event can still have considerable profits from engaging in exercise programs. Cardiac rehabilitation, including exercise programs can significantly lower mortality and incidence of recurrent episode in patients surviving myocardial infarction (MIN) (Kachur et al., 2017; Suaya, Stason, Ades, Normand, & Shepard, 2009; Witt et al., 2004) and markedly alter the prognosis of heart failure (Kondamudi et al., 2017).

Finally, apart from its vital importance in cardiovascular health, exercise and physical activity merits are also met in respiratory diseases. Chronic obstructive pulmonary disease (COPD) is probably the most prevalent respiratory disease in middle aged and older adults. Lifelong

exercise has been associated with reduced risk for COPD incidence in this population group in a study enrolling Japanese participants (Hirayama, Lee, & Hiramatsu, 2010). Moreover, lower physical activity for the first month following hospitalization due to an acute exacerbation is associated with increased risk for readmission within the next year.

This evidence underlines that exercise is of vital importance in preventing and detaining cardiovascular and pulmonary disease. Nevertheless, it is only a brief reference of the large amount of literature existing and future studies will certainly shed light in controversial issues.

2.2.2. TYPE 2 DIABETES MELLITUS AND CARBOHYDRATE METABOLISM

Physical activity has a further contribution in cardiovascular health by preventing and modifying the progression of type 2 diabetes mellitus (T2DM). Evidence indicative of this statement exist over the past two decades. Also, an association between increased physical activity and prevention of non-insulin resistant T2DM was found while individuals in highest risk had a more pronounced benefit. Where, an analysis in subjects of a large cohort including more than 70,000 women of age 30-55 years and without history of diabetes or cardiovascular disease and showed an inverse association between greater physical activity, attributed to an increase in the duration or intensity, and the risk for incident type 2 diabetes. These numbers suggest that vigorous exercise is more protective against moderate-intensity physical activity. Nevertheless moderate levels also assist considerably in T2DM prevention. In addition, walking can be of important assistance in reducing the risk for T2DM, and this reduction seems to be pace-related (Hu et al., 1999). Another study in middle aged Finnish men and women associated several forms of physical activity with lower probability of T2DM. Of note, LTPA in moderate and high intensity was associated with RR reduction of

33% and 39% respectively, for incidence of T2DM. Higher levels of LTPA have also been reported as preventing factor for diabetes in other studies (Haapanen, Miilunpalo, Vuori, Oja, & Pasanen, 1997; Wannamethee, Shaper, & Alberti, 2000). One reasonable explanation is that this material effect is mediated, to a significant extend, by reducing the risk for metabolic syndrome. Where, a significant inverse association demonstrated between moderate and vigorous LTPA (≥7.5 and ≥4.5 METs respectively) for ≥3h/week, in comparison with sedentary individuals, and the diagnosis of metabolic syndrome.

Exercise and PA have also been proven as substantial modifiers of diabetes' progression and long-term prognosis in terms of cardiovascular risk. These beneficial effects mainly originate from a better glycemic control and weight control. The Health Professionals Follow–up Study associated vigorous PA of ≥3h/week, with significan t decreases in HbA_{1c} and con-currently 22% risk reduction for myocardial infarction, potentially also mediated by a better glycemic profile. Larsson et al 2011 reported that both lower and moderate levels of self-reported LTPA lead to significantly lower insulin resistance compared to sedentarily spent leisure time. However, these studies were not conducted in an exclusively diabetic population. A positive linear association found, between the increase of the daily step count and improved insulin sensitivity studying a population of middle aged men and women. Furthermore, it has been reported that including PA in every day routine can be at least as effective as treating T2DM with a single pharmacological agent (Burr, Rowan, Jamnik, & Riddell, 2010).

There is rich evidence supporting the usefulness of aerobic, resistance, and combined structured exercise in accomplishing an improved glycemic control. Decades ago, it was reported that initiating sessions of aerobic exercise in daily life can aid in stabilizing HbA_{1c} levels in diabetic participants without however reducing HbA_{1c} levels. Such evidence emerged from other studies (Mourier et al., 1997) with qualitatively consistent results when

exercise frequency or intensity (Mourier et al., 1997) was increased. Another study (van Dijk, Tummers, Stehouwer, Hartgens, & van Loon, 2012) assessed whether a daily exercise pattern is more efficient than an every other day one, demonstrating similar but significant reduction in fasting plasma glucose in both patterns. It is also interesting, that short lasting sessions of cycling at 60% peak power followed by short resting breaks have been shown to lead in elevated insulin sensitivity. Such a model would comfortably fit older or obese individuals incapable of participating in more demanding exercise models (Hood, Little, Tarnopolsky, Myslik, & Gibala, 2011). A meta-analysis including trials designed to compare different exercise modalities associated higher intensities with lower HbA_{1c} compared to lower or moderate intensities. There was no consistency in results when fasting plasma glucose and insulin was assessed.

Resistant training has also been proposed as a useful alternative in order to accomplish better glycemic status in diabetic patients. Several studies and RCTs have associated resistance training models with modifications in glycemic indices, demonstrating at least stabilizing (Honkola, Forsen, & Eriksson, 1997) or altering effects. In particular, first proposed that a moderate intensity resistance training model can significantly decrease HbA_{1c} in diabetic people. RCTs published next years noted that resistance exercise in moderate or high intensity can contribute in significantly lowering HbA_{1c} and this material effect was mainly attributed to increased lean body mass (Baldi & Snowling, 2003; Castaneda et al., 2002; Dunstan et al., 2002). Apart from the increase in muscle mass and glucose uptake, it was suggested other mechanisms including changes in protein pathways can also play a role in this observed improved glucose uptake.

The aforementioned literature is conclusive in a considerable degree that aerobic and resistant training, when performed as a single exercise method, both have beneficial results in diabetic patients in terms of glycemic control. There is evidence supplied by several studies that the

combination of these two exercise forms is potentially equal or even more beneficial for diabetic patients. In a study where participants performed a combined, exercise program of moderate intensity for 1 year, results showed a significant lower fasting glucose levels. Qualitatively similar results emerged from other studies which implemented shorter and more intense models of combined exercise (Tokmakidis, Zois, Volaklis, Kotsa, & Touvra, 2004). And the effect of all three exercises in HbA_{1c} compared with a control group, demonstrating significant reductions in all experimental arms while the highest reduction was noted in the combined exercise group. Finally, combined exercise training has been shown efficient in decreasing HbA_{1c} levels, as well other cardiovascular risk factors, in the Italian Diabetes and Exercise Study (IDES) (Balducci et al., 2010).

2.2.3. EXERCISE, BONE MASS AND OSTEOPOROSIS

A large amount of literature describes the relationship of exercise and physical activity with bone mass and osteoporosis. Osteoporosis and osteopenia are quite prevalent and are usually met in older individuals and postmenopausal women (Tian et al., 2017; Wright et al., 2014). Apart from pharmaceutical treatment, exercise interventions and PA have notable effect on delaying and stabilizing bone mass diminution, or even stimulate increases in bone mass. The underlying mechanism that leads to these alterations is the stimulation of bone mass production attributed to the impact of mechanical forces in bone cells (Morseth, Emaus, Wilsgaard, Jacobsen, & Jorgensen, 2010). Such forces originate from the interaction with ground while performing exercise and the effects of muscle contractions on bone tissue mediated by tendons (Morseth et al., 2010). However, not all exercise forms and intensities act equally in bone mass. High-impact activities (e.g. volleyball, basketball, weight-lifting) are associated with significantly increased levels of BMD compared to low-impact exercises

(e.g. swimming, running) and non-exercisers. Another important finding, indicates that higher frequency, when combined with lower impact exercise, cannot counterbalance the loss of high-impact exercise benefits in BMD. Moreover, the effect of resistant training in BMD seem to be restricted in lumbar spine opposing to the femoral neck (Martyn-St James & Carroll, 2006, 2009) while mixing modalities affects positively both bone areas (Martyn-St James & Carroll, 2009). These data indicate that the type and degree of exercise impact act as modulatory factors in final effect in bone mass.

In patients with proven osteoporosis or high rates of bone absorption such as postmenopausal women, various exercise and PA modalities have been assessed as potentially beneficial for stabilizing or reversing this process. Walking, the most simple way of physical activity, has shown limited or neutral effect, as it possibly helps in preserving BMD only in femoral neck with no impact in spine (Ma, Wu, & He, 2013; Martyn-St James & Carroll, 2008). Other evidence about whether walking could assist in preserving bone mass in osteoporosis is discouraging. On the contrary, resistant and impact training can be very helpful in slowing or reversing the bone mass declines in older and postmenopausal women (Bolam, van Uffelen, & Taaffe, 2013). Interestingly, engaging in combined modalities (including aerobic, resistance, balance and other types of exercise) (Benedetti, Furlini, Zati, & Letizia Mauro, 2018) is associated with bone mass increase or at least stability in high risk groups. Also a multicomponent exercise model is able to increase BMD in lumbar spine compared to control individuals. Similar findings showed that multicomponent exercise can lead to significant increase in femoral neck BMD in older men.

2.2.4. EXERCISE AND CANCER

Although physical activity is not an established factor for the prevention of cancer, the association between PA and exercise training and the development of some cancer forms has been adequately described in literature. The most research has been done on colon and breast cancer. Approximately two decades ago the existing data reported a reduction of 40-50% in colon cancer among physically active people with no regard to gender. Significant risk reductions were also reported for breast cancer in women but not all studies were consistent. A more recent meta-analysis by (Wolin, Yan, Colditz, & Lee, 2009) including 52 studies demonstrated an 25% an 20% lower risk for incident colon cancer in men and women respectively. Similar association has been described between physical activity and breast cancer in pre and postmenopausal women (Eliassen, Hankinson, Rosner, Holmes, & Willett, 2010; Fournier et al., 2014; Wu, Zhang, & Kang, 2013). An inverse association between various PA modalities and intensities is reported in a meta-analysis, but this effect seem to be mediated by weight reduction attributed to a more active profile. These associations are possible explained by the modulatory effect of exercise in various biomarkers such as hormones (insulin, estrogens), inflammation markers, the pathway of apoptosis and others (Winzer et al., 2018). Apart from the preventing effect of PA, patients diagnosed with some types of cancer can also benefit by being active (Arem et al., 2015; Holick et al., 2008; Holmes, Chen, Feskanich, Kroenke, & Colditz, 2005).

2.2.5. EXERCISE AND MENTAL DISORDERS

The vital benefits of exercise and physical activity in human health are not restricted to organic disorders as there is evidence supporting that mental and psychological disorder can be prevented or managed in a better way with the assistance of exercise. Performing structured training can mitigate clinical manifestations of depression in symptomatic patients

(Craft & Perna, 2004). Mechanisms and hypotheses suggested as potential mediators are the increase of body temperature in particular brain territories leading to a sense of relief, the increase levels of endorphins and hormones such as serotonin which are mood stimulators. Moreover, the temporal distraction of burdening thoughts and the promotion of self-esteem through the sense of achievement coming from exercise activities are also contributing in the antidepressant effects of exercise (Craft & Perna, 2004). Engaging in exercise activities, even in moderate intensity can significantly lower the risk for developing depression. Participating in small duration aerobic exercise programs has been shown to improve symptoms in schizophrenic patients when combined with medical treatment (Wang et al., 2018). Consistent findings, also show that aerobic exercise can improve the quality of life of patients suffering by panic disorder by it cannot substitute medical interventions.

2.3. SMOKING AND DISEASE

Smoking is a very common and addictive habit and could easily be characterized as an epidemic taking into account epidemiological data from large organizations. The 2015 National Health Interview Survey (NHIS) reported a 20.1% total proportion of US adults that make use of one of tobacco products available. The most popular product was cigarette (15.1%). Recent data from World Health Organization (WHO) show decreasing rates of smoking the last decade but the percentage of smokers remains substantial (Onor et al., 2017).

2.3.1. SMOKING AND CARDIOVASCULAR DISEASE

The adverse effects of tobacco smoking in the cardiovascular system are probably the most well-known and consequential among its alterations in human health. Cigarette smoking is reported as the main preventable causal factor of CVD morbidity and mortality and accounts for approximately 20% of deaths annual in the U.S. (Onor et al., 2017). Smoking has been blamed to contribute in a plethora of vascular diseases (e.g. CHD, myocardial infarction, stroke, peripheral arterial disease, aortic disease and aneurysms) and cardiovascular disease mediating factors (hypertension, dyslipidemia, diabetes and others) (Benowitz & Burbank, 2016). Smoking has been proposed as the most important risk factor for MIN in young aged, and demonstrated the strong association of smoking and stroke. Of note there is an evident dose-dependent relationship of cigarette smoking and stroke risk (Shah & Cole, 2010; Shinton & Beevers, 1989). Consistent association has been described between smoking and development of peripheral arterial disease with a clear dose-dependent risk elevation (Willigendael et al., 2004).

Nicotine, the most famous among cigarette's ingredients, is believed to interact with the heart and vessels by various mechanisms (Benowitz & Burbank, 2016). Through stimulating catecholamine secretion, nicotine leads to increased BP levels, myocardial contractility and cardiac output. The effect of nicotine in coronary flow is controversial, whilst there is a clear relationship between cigarette smoking and the risk for coronary vasospasm and angina episodes. Myocardial tissue remodeling predisposing for heart failure, arrhythmogenesis susceptibility, endothelial dysfunction, thrombogenesis and arterial wall inflammation promoting atherosclerosis are extra mechanisms of nicotine induced CVD.

Finally, the well-established association of smoking and CVD is also evident by the better prognosis of patients with known CVD or history of a serious CV event after smoking cessation (Armstrong et al., 2014; Gerber, Rosen, Goldbourt, Benyamini, & Drory, 2009).

2.3.2. SMOKING AND RESPIRATORY DISEASE

Cigarette smoking is involved in the pathogenesis of various diseases of the respiratory system and it can be a determinant prognostic factor for prognosis and survival (Feldman & Anderson, 2013). The association of smoking with chronic obstructive pulmonary disease is well-established as smoking along with aging are the most important risk factor for the development of COPD (Buist et al., 2008). Studying a Swedish cohort, reported that despite an estimated 8%-15% proportion of COPD when examining patients >45 years, the percentage of elderly smokers with developed COPD was 50%. The prognosis of COPD is inseparably related with patient's smoking status as terminating this habit can substantially reduce COPD exacerbations. This is clear in the results of a study in a large cohort, where also demonstrated a linear association between the duration of smoking abstinence and reduction in exacerbation risk. Interestingly, those who quited smoking for 10 years or more had a 35% lowered risk to experience an acute exacerbation. Furthermore, active smoking predisposes to viral and bacterial respiratory infections which may trigger an acute exacerbation with potentially unfavorable prognosis (Decramer, Janssens, & Miravitlles, 2012). Pneumococcal pneumonia, various forms of viral pneumonia, Legionellosis and other respiratory infections are associated with smoking (Feldman & Anderson, 2013). It is remarkable that invasive pneumococcal pneumonia is more often encountered in active cigarette smokers compared to non-smokers (Nuorti et al., 2000).

2.3.3. SMOKING AND CANCER

The so-called causal association between tobacco smoking and lung cancer has been described in detail in a huge amount of literature. Lung cancer is almost exclusively

attributed to this habit as the proportion of men and women suffering from the disease and report cigarette abuse is 90% and 80% respectively (Walser et al., 2008). In general population, smokers have an estimated 30-fold higher risk to develop lung malignancy and the prognosis is usually poor (Walser et al., 2008). Of note, among total cancer mortality lung type holds a leading role and accounts for approximately one of three CA-attributed deaths in men and one of four in women. Furthermore, there is an evident increased risk for incidence of other cancer types in smokers e.g. oropharynx, laryngeal, tongue, esophageal liver, bladder, colorectal, cervical, pancreatic (Onor et al., 2017).

NICOTINE & BETA ENDORPHIN IN ADDICTION

Substance addiction and nicotine addiction, in particular, is based on specific criteria (Hatsukami, Stead, & Gupta, 2008) and presents a pattern of symptoms which makes it easily recognizable. Nicotine is the most well-known chemical substance among a wide variety of tobacco smoke ingredients due to a strong causal association with addiction (Berrendero, Robledo, Trigo, Martín-García, & Maldonado, 2010; Hatsukami et al., 2008). Despite a large variety in pharmacological mechanisms among abuse substances, considerable evidence indicates that when it comes to addiction, manifestations and underlying pathophysiology are quite common. Addiction is mediated by reward and the reinforcing effect of substances and is maintained by the adverse symptoms of abstinence as withdrawal (Nestler, 2005). The leading pathway involved in drug-induced reward is the mesolimbic dopamine pathway, mainly represented by dopaminergic neurons in ventral tegmental area (VTA) and the nucleus accumbens (NAc) (Nestler, 2005; Spanagel & Weiss, 1999). Other brain territories also participate in the reward process e.g. hypothalamus, amygdala, hippocampus, frontal cortex by interacting with VTA and NAc neurons.

Nicotine's properties are mediated by the activation of nicotine-acetylcholine receptors (nAchRs) (Benowitz, 2009; Jiloha, 2010; Nestler, 2005). These receptors are widely distributed in central nervous system (CNS) and mediate nicotine's involvement in plenty neurotransmitters' physiological activity e.g. dopamine, acetylcholine, noradrenaline, glutamate, GABA (Berrendero et al., 2010; Nestler, 2005). In CNS the highest reactivity degree in nicotine has been described for the combination of $alpha_4$-$beta_2$ (a_4b_2) subunits (Jiloha, 2010). It is of interest that when nicotine use is chronic and repetitive, physiological alterations occur in nicotine receptors i.e. desensitization of existing receptors and formation of novel (up-regulation) to counterbalance this phenomenon (Collins, Luo, Selvaag, & Marks, 1994; Jiloha, 2010; Wonnacott, 1990).

Inhaled nicotine, similarly with other addictive drugs, inserts in the brain parenchyma and activates nAchRs which are widespread in the mesolimbic system, inducing dopamine release and particularly elevated extracellular dopamine levels in NAc (Benowitz, 2009; Berrendero et al., 2010; Jiloha, 2010; Mansvelder & McGehee, 2002; Nestler, 2005). The rewarding effects of this interaction maintain the need to smoke. Despite this primary, mostly direct way of altering brain dopamine, the precise nicotine effect in mesolimbic dopamine levels is actually multicomponent. Other neurotransmitters such as glutamate and GABA are also physiologically connected with dopamine in brain and dopamine release is also augmented by the glutamate enhancement and GABA inhibition attributed to nicotine (Benowitz, 2009; Jiloha, 2010; Mansvelder & McGehee, 2002; Nestler, 2005). In addition, tobacco smoking has been associated with dopamine increases by reducing brain monoamine oxidase A(MAO-A) and B(MAO-B) which are responsible for dopamine deconstruction (Lewis, Miller, & Lea, 2007).

The endogenous opioid system is involved in the reward circuit as stimulation of μ and δ opioid receptors triggers dopamine release from particular brain territories (Berrendero et al.,

2010; Gianoulakis, 2004). Focusing on β-E, this particular peptide is a potent stimulant of these receptors and as mentioned in the reviews of Roth-Deri (Roth-Deri, Green-Sadan, & Yadid, 2008) and Trigo (Trigo, Zimmer, & Maldonado, 2009), stimulation of μ receptors by β-E facilitates dopamine production by VTA and NAc neurons. In addition to this direct pathway, β-E interacts with μ-receptors localized at GABA-ergic neurons in VTA inhibiting the normal dopaminergic attenuation caused by these cells. It is interesting that the reverse interaction between dopamine and β-E has been proposed, as dopamine acutely increased brain β-E levels in a study conducted in rats (Roth-Deri et al., 2003).

Evidence from animal studies has pointed that acutely administrated nicotine triggers β-E increases in brain (Boyadjieva & Sarkar, 1997; Marty, Erwin, Cornell, & Zgombick, 1985).

Stress is strongly associated with drug addiction, including nicotine, and is considered to importantly increase vulnerability for withdrawal symptoms and relapse (Sinha, 2008). The activation of the HPA axis is a primary biological response to acute stress (Richards et al., 2011). Apart from the alterations on this hormonal sequence related to nicotine use and addiction (see in following section), a small number of studies have given implications towards a more complicated involvement of the HPA axis in addiction including a reverse modulatory effect. It has been proposed that lower reactivity of cortisol secretion can predispose to experimentation of addictive substances like marijuana in young ages (Moss, Vanyukov, Yao, & Kirillova, 1999). Also, increased cortisol reactivity associated to stress with smoking progression within a 6-month follow-up period. Moreover, increased stress reactivity, as documented by cortisol levels, was related with susceptibility to relapse. Interestingly, this association was apparent only in men. Although these results set important implications about the connection of HPA axis and addiction, subsequent independent replication is needed to form strong evidence. Another important part of reaction to stress is

activation of the autonomous nervous system (ANS). To date, literature does not provide any important correlation between ANS function and vulnerability to smoking initiation or addiction.

2.3.4. SMOKING AND THE HPA AXIS

ACUTE SMOKING

Nicotine intake triggers an acute activation of the HPA axis and research endorsing this statement is rich (Richards et al., 2011; Rohleder & Kirschbaum, 2006). Results from basic research indicate that this stimulation is strictly localized in CNS (Cam, Bassett, & Cairncross, 1979; Weidenfeld, Bodoff, Saphier, & Brenner, 1989). Even more specifically, CRH release from the hypothalamus is a prerequisite for pituitary ACTH secretion (Marty et al., 1985; Matta, Beyer, McAllen, & Sharp, 1987). Furthermore, despite the general perception that nicotine acts directly on hypothalamic PVN, this interaction is mediated by an initial stimulation of brainstem nAchRs and secondary innervation of PVN. The above associations have been proven to be dose-dependent (Mendelson, Sholar, Goletiani, Siegel, & Mello, 2005; Rohleder & Kirschbaum, 2006) whilst studies in small samples of smokers demonstrated that two cigarettes are an adequate quantity to provoke the HPA axis (Kirschbaum, Wust, & Strasburger, 1992; Pomerleau & Pomerleau, 1990).

HPA AXIS IN HABITUAL SMOKERS

The picture in terms of the HPA axis function in chronic smoking is quite unclear as existing studies provide controversial results. As, similar plasma cortisol levels between two 6-subject groups of smokers and non-smokers. Or, differences in plasma cortisol between active

smoking and abstinence, as that 24-h urine cortisol is not affected by chronic smoking. Still, considering the pattern of cortisol secretion within the day, the latter results are not likely to make a clear point. However, small number of participants and intermittent smoking within sample receiving comprise important limitations to these results, as a significant positive association between basal HPA axis function and habitual smoking was reported. Although significant increases in cortisol requires a lower limit of 20 cigarettes per day. Summarizing the above it remains unclear if chronic smoking alters basal HPA axis function and it has not yet been elucidated whether the increased activity reported by some authors is attributed to long-term tobacco use or a temporal effect of cigarettes smoked during a day.

In contrast with the controversy about the relationship of chronic smoking and basal HPA axis function, in the field of reactivity to stress current evidence is in favor of a blunted HPA axis response to stress stimuli. Five studies addressed this issue and consistently concluded that habitual smokers have blunted reactivity of the HPA axis in psychological stress (Back et al., 2008; Buchmann et al., 2010; Childs & de Wit, 2009; Kirschbaum, Strasburger, & Langkrar, 1993) by assessing the differences in cortisol between smokers and non-smokers following a stress stimulus. It has to be clear that according to these studies, smoking does not abolish the ability of the HPA axis to answer in acute stress (Buchmann et al., 2010) but the magnitude of this reactivity is limited in long-term cigarette users. Furthermore, Rohlender and Kirschbaum, (2006) and Back et al. (2008) reported a sex disparity in cortisol responses in stress since in both studies female gender was associated with lower reactivity. Still, this implication needs further investigation.

2.4. CATECHOLAMINES

EXERCISE-SMOKING AND CATECHOLAMINES

Acute smoking has had a causal association with catecholamines release since decades. This has been seen both in vitro, where nicotine stimulated catecholamine secretion from adrenal glands in rats (Mizobe & Livett, 1983) and in small cohorts of human subjects (Cryer, Haymond, Santiago, & Shah, 1976; Grassi et al., 1994; Mundal, Hjemdahl, & Gjesdal, 1998). In chronic nicotine consumption, current perception is that basal norepinephrine levels are elevated, representing a higher sympathetic nervous system (SNS) arousal, opposing to a blunted catecholamine release after acute nicotine administration (Richards et al., 2011).

Summarizing and explaining accumulating amount of literature the authors concluded that: i) Acute exercise leads to elevated catecholamine levels in blood and intensity and duration are important determinants of this association (Jacob et al., 2004; Moussa et al., 2003; Zouhal et al., 2001), ii) Evidence about resting catecholamines' in trained individuals are controversial, iii) Engaging in aerobic exercise in a routine-like manner is associated with increased adrenal medullary hormone release after an acute bout and this mainly addresses to men, iv) In agreement with aerobic, anaerobic training modulates adrenal reactivity to acute exercise leading to higher adrenaline levels compared with untrained individuals, v) An apparent sex disparity in terms of catecholamine responses, as men exhibit hormone elevations regardless of training status, while in women literature did not provide consistent data.

2.5. BETA-ENDORPHIN

2.5.1. PHYSIOLOGY

Beta-endorphin (β-E) belongs to the family of endogenous opiate peptides. It is the derivative of metabolism and cleavage of a larger precursor peptide named pro-opiomelanocortin

(POMC). POMC is a composite protein since its molecule contains several hormones such as MSH, adrenocorticotropic (ACTH), β- and γ-lipoprotin. β-lipoprotin, after undergoing cleavage gives two derivatives, β-endorphin and gamma-endorphin (Dalayeun, Nores, & Bergal, 1993). Two separate systems of POMC production have been described. The first system, constitutes the source of brain β-E and is located on the hypothalamic arcuate nucleus (ARH) while peripherally circulating β-E is derived from POMC molecules which are produced in the anterior and intermediate pituitary lobe, especially in the latter one (Veening, Gerrits, & Barendregt, 2012). Of note these systems are considered to have independent functionality. In a narrative review, Veening et al., (2012) summarized a considerable amount of studies and suggested that brain β-E is almost completely unaffected by pituitary function, plasma concentrations are substantially lower than those in cerebrospinal fluid (CSF), indicating that it is unlikely that blood peripheral β-E modulates central levels and brain β-E undergoes minimal degradation while plasma peptides have short half-life times both in animals and humans. Still, blood-brain barrier (BBB) might not present total integrity as after peripheral infusion of β-E in rabbits, CSF levels showed a gradual, delayed increase. Furthermore, collateral vascular connections between the pituitary and brain parenchyma possibly mediate the transmission of pituitary derived β-E in CSF circulation (de Kloet, Palkovits, & Mezey, 1981; Oliver, Mical, & Porter, 1977).

Among the three major types of opioid receptors (μ, κ, δ), β-E presents an equal degree of affinity with μ and δ receptors while it does not interact with κ receptors (Gianoulakis, 2004). Several studies have described the involvement of β-E in different pathophysiological paths including the mechanism of pain production as well as in many neurological and psychiatric disorders (Dalayeun et al., 1993).

2.5.2. EXERCISE AND BETA-ENDORPHIN

The association of different exercise modalities and β-endorphin levels has been an issue of considerable amount of research two decades ago with several studies reporting different correlations and sometimes equivocal results. Unfortunately, there are no available studies conducted within the recent years and there seems to be a gap in literature with regard to the exact associations of exercise and β-endorphin levels in plasma. The summary perspective is that exercise in different modalities leads to increases in plasma β-endorphin concentrations (Goldfarb & Jamurtas, 1997). Regarding aerobic exercise, various studies have demonstrated the association of acute bouts and increases in β-endorphin and other hormones (de Meirleir et al., 1986; Farrell, Kjaer, Bach, & Galbo, 1987; Goldfarb, Hatfield, Armstrong, & Potts, 1990; Goldfarb, Hatfield, Potts, & Armstrong, 1991; McMurray, Forsythe, Mar, & Hardy, 1987; Rahkila, Hakala, Alen, Salminen, & Laatikainen, 1988). However, this impact is delivered only beyond specific limits of intensity. Interestingly, these studies pointed that the anaerobic threshold must be reached to note significant acute alterations in β-E. Aerobic exercise has the more evidently supported association with increased β-E release in plasma, given that critical intensity is achieved (Goldfarb & Jamurtas, 1997). There is no consistency regarding resistance exercise as studies' results are controversial (Goldfarb & Jamurtas, 1997). In detail, a neutral effect of resistance exercise in β-E in a sample or resistance trained participants, was observed, on the other hand a negative association of RE and β-E when they implemented a multitasking resistance program in 20 college students. On the contrary RE associated with post exercise elevations in β-E while the same team in a following study reported that high total RE volume is required to increase plasma b-E (Kraemer et al., 1993). The above studies are summarized in Table 2.

Table 2. Studies about the effect of acute aerobic and resistance exercise on beta-endorphin levels.

Study ID	Subjects	Intervention type	Results-Conclusion
Aerobic exercise			
de Meirleir et al. (1986)	14 human volunteers	Bicycle ergometer below anaerobic cut-off and high intensity	Acute exercise increases β-endorphin and ACTH only above anaerobic cut-off
Farrell et al. 1987	7 endurance trained & 7 untrained subjects	Treadmill running, i)60% VO_2max, ii)100% VO_2max, iii)110 VO_2max	Acute increases in β-endorphin and ACTH only for ii) (similar between groups) & iii) (higher in trianed).
McMurray et al. (1987)	10 men & 10 women	Bicycle ergometer, 20min, at 40%, 60%, 80%VO_2max	Aerobic exercise increases β-endorphin only above 80% VO_2max
Rahkila et al (1988)	10 endurance male athletes	Treadmill running	Beta-endorphin increase only above 90% VO_2max. Anaerobic response needed in endurance athletes
Goldfarb et al. (1990)	12 college-aged men	Bicycle ergometer, 30min, 60%, 70%, 80% VO_2max	Aerobic exercise increases β-endorphin only above 70% VO_2max
Goldfarb et al. (1991)	6 trained and 6 untrained individuals	Bicycle ergometer, 60%, 70%, 80% VO_2max	Aerobic exercise increases β-endorphin only above 70% VO_2max
Resistance Exercise			
Walberg-Rankin et al. (1992)	5 female recreational weightlifters	85% RM, 10-12 reps	Resistance exercise elevated β-endorphin only after negative energy balance
Pierce et al (1993)	6 resistant-trained athletes	Isotonic exercise, 3 sets-8reps, 80% max. effort	No significant post-exercise β-endorphin levels
Pierce et al (1994)	10 male-10 female college students	Multi-exercise isotonic program	Decreased post-exercise levels of β-endorphin
Kraemer et al. (1992)	28 junior, male, elite weightlifters	Moderate to high intensity, low volume weightlifting	Post-exercise β-endorphin increases independent to training years
Kraemer et al. (1993)	8 male individuals	Six resistance exercise protocols	Only the high-total work protocol elicited β-endorphin

	(5-10reps), (rest:1-3min), total work	elevation

The landscape is also unclear in terms of β-E levels in trained individuals. According to Goldfarb and Jamurtas (1997), various studies have shown inconclusive results. For instance, long-term aerobic training has been described to have neutral (Farrell et al., 1987; Goldfarb et al., 1991; Howlett et al., 1984; Pierce, Eastman, Tripathi, Olson, & Dewey, 1993) and negative effect on resting β-E levels (Lobstein & Ismail, 1989; Lobstein & Rasmussen, 1991). Performing an acute bout of aerobic exercise in trained population has shown to increase (Carr et al., 1981; Farrell et al., 1987; Mougin et al., 1988), decrease (Kraemer et al., 1989; Metzger & Stein, 1984) or not significantly alter β-E levels (Farrell et al., 1987; Goldfarb et al., 1991; Howlett et al., 1984). Finally, the evidence about β-E levels in resistance trained people is scarce (Kraemer et al., 1992; Pierce et al., 1993) and further research is necessary to establish a strong association.

2.6. THE HYPOTHALAMUS-PITUITARY-ADRENAL (HPA) AXIS

The hypothalamo-pituitary-adrenal (HPA) axis is one of the major components of human endocrine system as it is involved in various physiological and metabolic pathways. The predominant final products of this axis are glucocorticoids (GSs) and mainly cortisol. The physiology and the separate signaling stages of the HPA axis are well-known. Briefly, neurons in the hypothalamic periventricular nucleus secrete corticotrophin releasing hormone (CRH) and this peptide stimulates the anterior pituitary lobe to release adrenocorticotropic hormone (ACTH) in systematic circulation (Stephens & Wand, 2012). ACTH, in turn, triggers cortisol release from zona fasciculata cells. In order to preserve balance in this

system, peptide derivatives of each level initiate their own inhibition (Stranahan, Lee, & Mattson, 2008). Furthermore, circulating cortisol provide negative feedback to the pituitary gland and hypothalamus. The HPA axis is summarized in Figure 1.

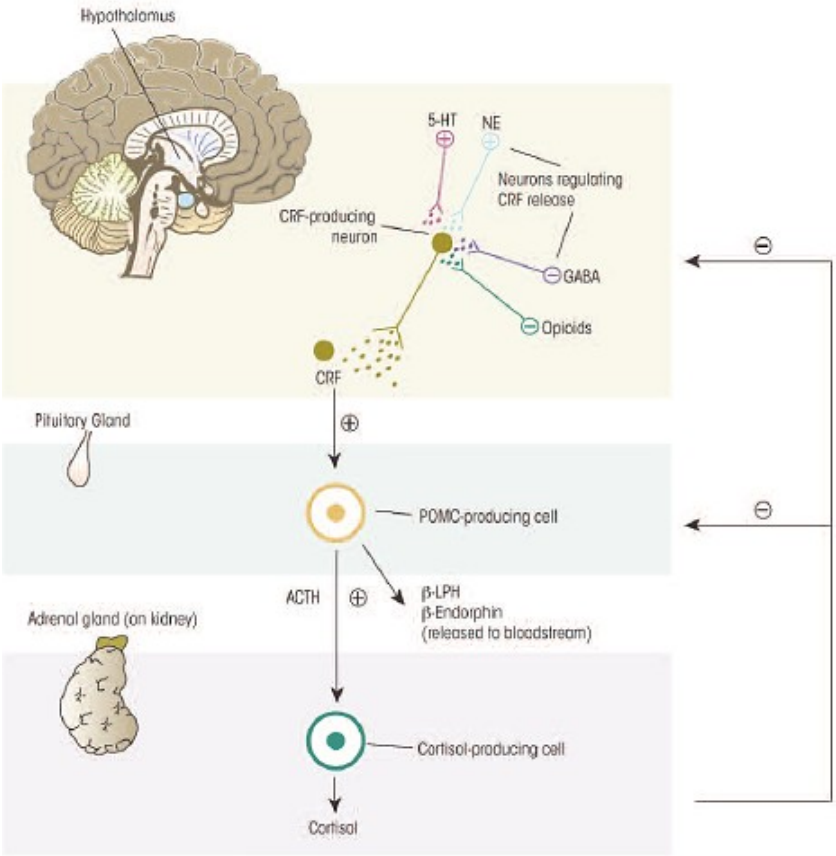

Figure 1. The hypothalamic-pituitary-adrenal (HPA) axis (Stephens & Wand, 2012).

2.7. EXERCISE AND THE HPA AXIS

The vast majority of research about the effects of exercise on the HPA function and the HPA related hormones has been conducted on animals. In humans, to describe precisely the associations between exercise and HPA and all the related parameters requires interventional

studies and their applicability in large human samples is quite poor. As a result, the number of existing studies is limited.

Exercise has strong stimulant action on HPA axis, mainly localized in the initial part at the hypothalamus (Timofeeva, Huang, & Richard, 2003). In this study, investigators found an increased neuronal activity in cells of the periventricular nucleus (CRH-producing unit) in rat brains, following a 90-minute treadmill running.

Consistent reactivity of the HPA axis has been observed in human subjects following acute bouts of exercise with no regard to the exercise type (Duclos & Tabarin, 2016). In particular, aerobic exercise of moderate (MI) and high intensity (HI) increased salivary cortisol in a sample of 26 young, moderately active subjects (Scerbo, Faulkner, Taylor, & Thomas, 2010). After aerobic exercise, HPA axis hormones' increases occur irrespectively of training status, given that an intensity threshold of 70% VO_2max is achieved. Also, basal levels of the HPA hormones are higher in trained individuals. Moreover, endurance trained and sedentary subjects both exhibited increased ACTH and cortisol levels after participating in an aerobic program. Still, these alterations were noted only after a long-lasting and intensive exercise program, strengthening the idea that aerobic training stimulates HPA hormone secretion independently of physical conditioning. Similar effects have been described for resistance models of exercise (Duclos & Tabarin, 2016; Ho et al., 2014). Apart from intensity, other factors can also modulate this response. Results from the past decades indicate accelerated cortisol response in hypohydrated individuals after resistance exercise (Judelson et al., 2008), while postprandial HPA responses to exercise were diminished. Moreover, as normal HPA hormones secretion follows a specific pattern, the magnitude of HPA responses in acute exercise varies within the day times. Also, cortisol found to response to acute treadmill running was significantly elevated at midnight compared to the first day hours (07:00) and evening hours (19:00). In a second bout of acute exercise, the duration of the intermediate

recovery period is a modulating factor for the magnitude HPA response noting higher ACTH and cortisol levels after shorter resting period.

Despite the potent acute post-exercise responses of the HPA axis, current knowledge does not reveal any dependency of long-term HPA activity on physical condition, as trained individuals who perform endurance training have similar resting hormones' levels compared to sedentary ones (Duclos & Tabarin, 2016). Nevertheless, as mentioned before, the latter population category does not preserve an intact reactivity to subsequent physiological stimuli (Ronsen, Kjeldsen-Kragh, Haug, Bahr, & Pedersen, 2002), whilst psychosocial stress has blunted influence on trained people (Klaperski, von Dawans, Heinrichs, & Fuchs, 2013).

2.8. EXERCISE AND SMOKING

2.8.1. ACUTE EXERCISE AND SMOKING

Many studies intended to enlighten the possible association between acute bouts of exercise and smoking urge in individuals willing to abandon this habit. Nowadays, there is remarkable evidence that aerobic exercise, in acute form, can provide temporary relief from smoking urge. Interestingly, this effect occurs independent of exercise intensity. Moderate intensity aerobic exercise on treadmill or cycling ergometer was associated, in various studies, with reduced desire for cigarette after the intervention completion (J. Daniel, Cropley, Ussher, & West, 2004; J. Z. Daniel, Cropley, & Fife-Schaw, 2006, 2007; Elibero, Janse Van Rensburg, & Drobes, 2011; Everson, Daley, & Ussher, 2008; Fong, De Jesus, Bray, & Prapavessis, 2014; Janse Van Rensburg, Taylor, Benattayallah, & Hodgson, 2012; Janse Van Rensburg & Taylor, 2008; Kurti & Dallery, 2014; Oh & Taylor, 2014; Prapavessis et al., 2014; Scerbo et al., 2010; M. Ussher, Nunziata, Cropley, & West, 2001; Van Rensburg, Taylor, & Hodgson,

2009). It is however unknown, whether the duration of this effect extends beyond a post-exercise short period. None of the aforementioned studies evaluated desire levels beyond 30 minutes. Of note, reductions in cigarette craving were present at the time endpoint of 30 minutes only in the study of Prapavesis et al. (2014). Some authors reported that moderate intensity interventions achieved reductions in craving up to 15-20 minutes (J. Z. Daniel et al., 2007; Elibero et al., 2011; Janse Van Rensburg & Taylor, 2008) while in other studies exercise's decreasing effects on smoking desire were non-significant or not measured after 10 minutes (J. Daniel et al., 2004; J. Z. Daniel et al., 2006; Everson et al., 2008; Scerbo et al., 2010; M. Ussher et al., 2001). Same associations have been described elsewhere despite time endpoints were not specified or desire was merely evaluated after the end of the intervention (Fong et al., 2014; Janse Van Rensburg et al., 2012; Kurti & Dallery, 2014; Oh & Taylor, 2014; Schneider, De Jesus, & Prapavessis, 2014). Aerobic programs of vigorous intensity consistently lowered cravings within available studies (Bock, Marcus, King, Borrelli, & Roberts, 1999; Everson et al., 2008; Oh & Taylor, 2014; Scerbo et al., 2010). Even in light intensity aerobic exercise was shown to be effective in temporary craving reductions (Faulkner, Arbour-Nicitopoulos, & Hsin, 2012; Janse Van Rensburg, Elibero, Kilpatrick, & Drobes, 2013; A. H. Taylor, Katomeri, & Ussher, 2005; A. H. Taylor, Ussher, & Faulkner, 2007). In regards to resistance training, two available studies report controversial results. In conclusion, there is abundant evidence that exercise is effective in reducing smoking urge in the acute phase. The above studies are summarized in Table 3.

Table 3. Studies on the effects of acute bouts of exercise in smoking desire.

Aerobic exercise				
Study ID	**Subjects**	**Interventions**	**Endpoint(s)**	**Results-Conclusions**
Pomerleau	10 inactive	30 min. cycling,	Smoking desire	No differences

(1987)	men	i)HI(80%VO_2max), ii)LI(30% VO_2max)	up to 20 min post-exercise	between light and high intensity
Thayer (1993)	5 men & 11 women	5 min. walking, i)brisk walk, ii)inactivity	i)Smoking urge, ii)time to next cigarette	i) reduced urge and increased time to next cig.
Bock (1999)	Two women groups: 1):24, 2):44	30-40 min. HI activity (65-80% HRR)	Post exercise cravings & withdrawal	Vigorous exercise reduced cravings and withdrawal
Ussher (2001)	78 inactive men & women	10 min. : i)MI cycling(40-60% HRR), ii)video, iii)passive	Smoking desire: i)post-exercise, ii)5 min., iii) 10min.	MI exercise reduced desire up to 10 min. post-exercise
Daniel (2004)	84 inactive men and women	i)5 min. cycl.-MI(40-60% HRR), ii)5 min. cycl.-LI(10-20% HRR), iii)passive	Smoking desire: i)post-exercise, ii)5 min., iii) 10min.	MI reduced desire up to 10min. compared to LI and control
Daniel (2006)	23 men & 17 women, all sedentary, non-quitters	i)10 min. MI cycl. (40-60% HRR), ii) passive control(Cognitive distraction task	Smoking desire: i)post-exercise, ii)5 min., iii)10min	MI reduced desire up to 10 min. compared to control
Taylor (2005)	10 men & 5 women: all active	i)LI, 1 mile treadmill walking (25% HRR), passive control	Smoking desire: i)post-exercise, ii)10 min., iii) 20min.	LI reduced desire up to 20 min. compared to control, increased time to next cigarette
Everson (2006)	19 men &18 women, non-quitters	10 min. cycling: i)55% HRR ii)44%HRR	SoD: i)5 min., i)30 min.	No differences between groups
Taylor (2007)	26 men &34 women, moderately active, non-quitters	i)15min. LI walking (24%HRR) ii)Passive control	i)Smoking desire: post-exercise ii)Time to next cigarette	LI walking reduced cravings, increased time to next cigarette
Daniel (2007)	22 men & 23 women, non-quitters	10 min. MI cycl.(40-60% HRR) i)Positive expectations	SoD: i)15 min. ii)20 min. (compared to	Significant reductions in desire in all groups

		ii)Neutral expectations iii)Negative expectations	pre-exercise)	
Everson (2008)	25 men & 20 women, non-quitters	10 min. cycling: i)MI(40-59% HRR), ii)HI(60-84% HRR), iii)Passive control	SoD: i)5 min. ii)30 min.	MI &HI exercise reduced desire only up to 5min.
Janse van Rensburg (2008)	15 men & 8 women, non-quitters	i)15 min. MI treadmill walking ii)passive control	Smoking desire: i)5min. ii10min., iii)15min.	MI walking relieved from desire up to 15 min. compared to control
Janse van Rensburg (2009)	13 men &3 women	i)15 min. MI cycling ii)Passive control	Smoking desire post exercise	(i)<(ii) for smoking desire post -exercise
Scerbo (2010)	10 men &8 women	15 min.: i)MI walking (45-50% HRR) ii)HI running(80-85% HRR) iii)Seating control	Smoking desire & SoD i)10min. ii)20min. iii)30min. post exercise	i)MI & HI exercise< control in SoD(MI only post-treatment, HI up to 10min. ii)MI &HI exercise< control for desire (MI up to 10min, HI up to 20min.)
Faulkner (2010)	11men & 8 women	10 min.: i)MI walking ii)Passive control	Smoking craving: i)post-exercise, ii)10min., iii)20min., Time to first cigarette	Walking did not reduce craving after completion. MI walking significantly increased time to first cigarette.
Elibero (2011)	76 subjects	30 min.: i)MI walking ii)yoga iii)Rest	Craving and cue reactivity to smoking images i)post-exercise ii)20min.	Brisk walking and yoga reduced craving and cue reactivity only post-exercise

Williams (2011)	60 women	8-week smoking cessation program i)Acute 50 min brisk walking ii)30 min. film viewing	Craving post-intervention	No significant differences between exercise and film viewing.
Janse van Rensburg (2012)	20 participants	10 min. i)MI cycling, ii)Passive control	Smoking desire and SoD post-intervention	MI cycling significantly reduced desire and SoD after completion
Janse van Rensburg (2013)	107 men, 55 women	20 min. i)LI treadmill running, ii)HI treadmill running, iii)Passive control	Smoking urge, cue reactivity to smoking and salivary cortisol post-intervention	Both LI &HI exercise reduced smoking urge compared to control. HI reduced desire after smoking cues(not cortisol-related).
Cooke (2014)	10 men & 12 women	10 min. i)MI treadmill walking, ii)Audio describing physical activity iii)Audio describing daily activities	SoD post-intervention	No significant reductions in SoD after exercise
Fong (2014)	11 men &14 women	15 min. i)MI treadmill walking ii)Sitting control	SoD & withdrawal post-intervention	Exercise reduced smoking desire and withdrawal compared to control
Kurti (2014)	15 men & 5 women	20 min. i)MI exercise(no details) ii)Sitting control	Smoking urges(questionnaire), delay to first cigarette	Exercise significantly increased time to first cigarette
Oh (2014)	15 men & 8 women	15 min. i)MI cycling ii)HI iii)Sitting control	SoD to smoke	Both moderate and vigorous exercise reduced SoD up to 10min post-exercise

Prapavesis (2014)	30 women	20 min. i)MI treadmill walking, ii)DVD watching	SoD &withdrawal i)Post-exercise ii)10min. iii)20min., iv)30min	Exercise reduced SoD & withdrawal up to 30 min. vs control
Schneider (2014)	14 men & 38 women	10 min. i)MI treadmill walking, ii)Passive control	Desire to smoke post-intervention	Exercise reduced desire to smoke vs control

Resistance exercise

Study ID	Subjects	Interventions	Endpoint(s)	Results-Conclusions
Ussher (2006)	33 men &27 women	5min. i)Isometric exercise ii) Passive control	SoD &withdrawal i)Post exercise ii)5min, iii)10min., iv)15min., v)20min.	i)Isometric exercise reduced SoD up to 5min. vs control. ii)Reduced withdrawal up to 20min post-exercise.
Ussher (2009)	31 men & 17 women	10min. i)Isometric exercise ii) Passive control	SoD &withdrawal symptoms up to 30min. i)In laboratory ii)In natural environment(NE)	Isometric exercise reduced SoD up to 30 min. in lab. &up to 5 min. in NE. Isometric exercise reduced withdrawal in both environments.

SoD: Strength of desire, **LI**: Light intensity, **MI**: Moderate Intensity, **HI**: High intensity, **HRR**: Heart rate reserve.

2.8.2. EXERCISE PROGRAMMS IN SMOKING CESSATION

A considerable amount of studies addressed the hypothesis that exercise programs or initiating and altering PA levels could be of assistance in smoking cessation attempts. The most attention has been paid on aerobic exercise. However, almost all of current studies assessed composite smoking-terminating interventions. In the first study, a 3 month aerobic program of moderate intensity, performed 3 times/w, was inferior to cognitive-behavioral treatment (CBT) in terms of smoking abstinence at the end of treatment (EOT). Abstinence rates were similar and the end point of follow-up (EOFU). The latter authors compared a walking program with behavioral training and results were in favor of control arm. MI aerobic exercise program did not alter the effect of CBT and nicotine replacement therapy (NRT) combination compared to control. Aerobic exercise of high (Kinnunen et al., 2008) and moderate intensity (Abrantes et al., 2014; Bize et al., 2010) as well as exercise counseling (Maddison et al., 2014; M. Ussher, West, McEwen, Taylor, & Steptoe, 2003, 2007) seemed to have neutral effect as an extra measure in subjects under NRT. Continuous smoking abstinence was higher when vigorous aerobic exercise was added to smoking cessation program and this association was noticed on the end of the treatment and on 12 months during follow-up. Other authors showed similar abstinence rates when aerobic exercise intervention was tested against smoking cessation programs (Hill, 1985; Marcus, Albrecht, Niaura, Abrams, & Thompson, 1991; Marcus et al., 1995; Russell, Epstein, Johnston, Block, & Blair, 1988; Whiteley et al., 2012). The initiation of an exercise program in post-MI patients decreased smoking prevalence compared to non-training group but this effect was not statistically significant (C. B. Taylor, Houston-Miller, Haskell, & Debusk, 1988) (Taylor 1998). A trend for higher abstinence rates after a 6-month yoga plus CBT study in 55 female subjects was found. However, even this trend was not observed at the EOFU. Finally, concerning resistance training, in a single study smokers randomized to the

exercise arm had non-significant differences in abstinence at EOT and EOFU. In summary, current evidence is not supportive of a beneficial effect of exercise in smoking cessation.

3. METHODOLOGY

3.1. SUBJECTS

Healthy non-systematically exercising individuals; 25 smokers (13 men, 12 women; age: 33±1.4 years; body mass index: 26.8±1.1 kg/m2; smoking cigarettes/day: 25.9±1.9; nicotine dependence: 6.5±0.4) participated in the study. Nicotine dependence was assessed by the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991). All subjects were informed about the study protocol, the associated risks and benefits and they signed an informed consent form.

3.1.1. INCLUSION CRITERIA

1) Habitual smokers (Smoking >10 cigarettes/day accompanied by smoking urge at the morning)
2) Smoking abstinence for 10-12h prior to each intervention and blood sampling
3) No other drug addiction
4) Age: 18-65y.

3.1.2. EXCLUSION CRITERIA

Medical disease or medication use (for at least 3 months), which render participation in aerobic exercise impossible.

3.2. EXPERIMENTAL DESIGN

The procedures were in accordance with the 1975 Declaration of Helsinki. Approval was received from the University of Thessaly review board. Participants underwent three trials [moderate intensity (MI) and high intensity (HI) exercise, control (C)] in counterbalanced order separated by at least six days. MI involved cycling at 50-60% of the Heart Rate Reserve (HRR; 126-138 beats/min) for 30 min, HI involved cycling at 65-75% of the HRR (144-157 beats/min) for 30 min, while in C participants rested quietly for 30 min. Data were collected in a thermoregulated laboratory (mean temperature 23.4±0.8ºC).

3.3. BLOOD COLLECTION AND HANDLING

Blood samples were drawn from a forearm vein and then were handled as follows:

- A small portion of blood was collected into ethylenediamine tetra acetic acid (EDTA) tubes and shaken thoroughly for the determination of complete blood count (CBC) and lactic acid (LAC).
- For preparation of plasma for β-E determination, another portion of blood was collected in vacutainer tubes containing EDTA and Trasylol® (5000 KIU Trasylol in a 10 ml vacutainer tube) shaken thoroughly and cooled in an ice-bath. Plasma was separated by centrifugation at 1370 x g for 10 min at 4ºC. The supernatant was transferred into Eppendorf tubes® and was immediately stored at 80ºC until assayed.

3.4. BIOCHEMICAL ASSAYS

All indices were measured twice on the same day, while samples had undergone only one freeze-thaw cycle. The assays and instruments used have been described in an earlier paper

from our laboratory (Georgakouli et al., 2017). Biochemical indices included β-endorphin, adrenocorticotropic hormone (ACTH), cortisol and catecholamines (epinephrine, norepinephrine and dopamine).

3.5. SMOKING URGE AND TIME TILL FIST CIGARRETE

Smoking urge was evaluated by asking participants how strong was their urge to smoke at that moment, in a scale from 1 (no urge) to 7 (extremely strong urge). They were asked before and immediately after exercise. Time till first cigarette was defined as the time they finished exercise till the first cigarette that they smoked.

3.6. STATISTICAL ANALYSIS

Data are presented as mean ± standard error (SE). Data were analyzed by using two-way repeated measures ANOVA [3 conditions (MI, HI, C) x 2 time points (pre-, post-exercise)]. If a significant interaction was obtained, pairwise comparisons were performed through simple contrasts and simple main effects analysis (Bonferroni test). Moreover, one-way repeated measures ANOVA was conducted to examine differences in time till first cigarette [(3 conditions (MI, HI, C)]. The level of statistical significance was set at $p<0.05$. The statistical program used was SPSS version 18.0 (SPSS Inc., USA).

4. RESULTS

Mean HR during MI was 131.6±4.5 beats per minute (bpm) and during HI was 145.2±7.8 bpm. Mean HR during C was 68.2±6.7 bpm.

SMOKING URGE AND TIME TILL FIRST CIGARETTE

Smoking urge did not differ between trials at baseline and did not change after any condition. There was a significant effect of condition for time till first cigarette [$F(2,48) = 4.57$, $p=0.015$]. Pairwise comparison showed that time till first cigarette was significantly increased ($p=.048$) after HI (20.1±5.1 min) compared to C (11.3±5.2 min).

HPA AXIS

Beta Endorphin

β-E levels were significantly increased both after MI and HI exercise program compared to pre-exercise levels while no changes were observed in the control arm. β-E was significantly higher after HI exercise compared to MI. β-E levels pre- and post-interventions are illustrated at **Figure 1**.

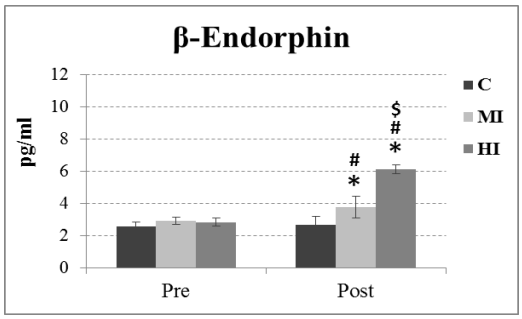

Figure 1. Beta-Endorphin levels prior and following each intervention arm. **Significant (p<0.05) difference with pre-exercise in the same exercise trial; [#]Significant (p<0.05) difference with C trial at the same time point in the same group; [$]Significant (p<0.05) difference with MI trial at the same time point in the same group.*

ACTH and Cortisol

ACTH and cortisol levels significantly increased only following HI exercise compared to pre-exercise state and control program. Significant increased were observed after the HI program compared to the MI one. ACTH and cortisol levels pre- and post-interventions are illustrated at **Figure 2** and **Figure 3** respectively.

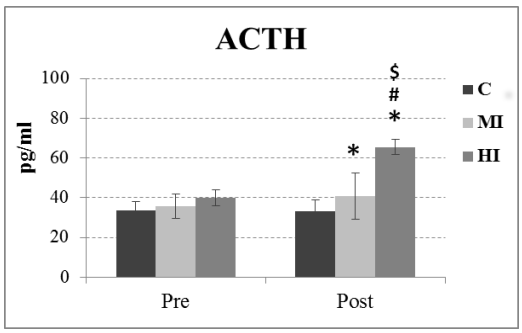

Figure 2. ACTH levels prior and following each intervention arm. **Significant (p<0.05) difference with pre-exercise in the same exercise trial; [#]Significant (p<0.05) difference with C trial at the same time point in the same group; [$]Significant (p<0.05) difference with MI trial at the same time point in the same group.*

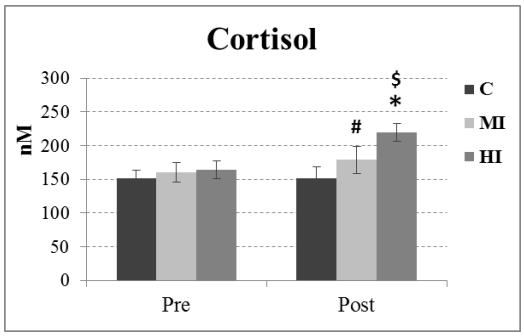

Figure 3. Cortisol levels prior and following each intervention arm. **Significant ($p<0.05$) difference with pre-exercise in the same exercise trial; [#]Significant ($p<0.05$) difference with C trial at the same time point in the same group; [$]Significant ($p<0.05$) difference with MI trial at the same time point in the same group.*

Catecholamines

Norepinephrine levels were significantly increased both after MI and HI exercise program compared to pre-exercise levels while no changes were observed in the control arm. Norepinephrine was also significantly higher after HI exercise compared to MI. Epinephrine levels were significantly increased both after MI and HI exercise program compared to pre-exercise levels while no changes were observed in the control arm. Epinephrine was significantly higher after HI exercise compared to MI. Catecholamine levels pre- and post-interventions are illustrated at **Figure 4** and **5**.

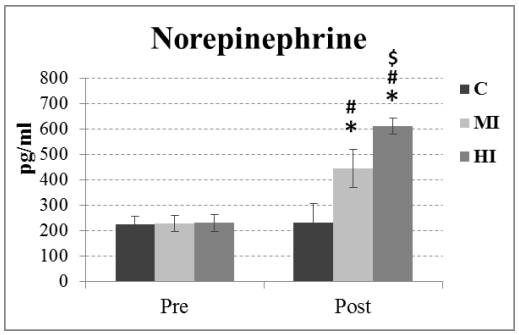

Figure 4. Norepinephrine levels prior and following each intervention arm. **Significant* *(p<0.05) difference with pre-exercise in the same exercise trial; #Significant (p<0.05) difference with C trial at the same time point in the same group; $Significant (p<0.05) difference with MI trial at the same time point in the same group.*

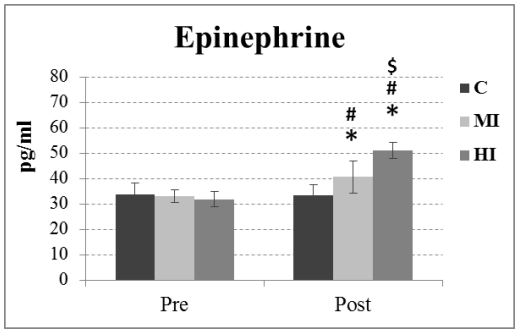

Figure 5. Epinephrine levels prior and following each intervention arm. **Significant* *(p<0.05) difference with pre-exercise in the same exercise trial; #Significant (p<0.05) difference with C trial at the same time point in the same group; $Significant (p<0.05) difference with MI trial at the same time point in the same group.*

5. DISCUSSION

The purpose of this study was to investigate whether acute exercise at different intensities causes changes in the activation of HPA axis that could be accompanied by changes in smoking behaviour. The results from this study indicate that intense exercise can delay the time to smoke a cigarette following an exercise bout and therefore decreasing the urge to smoke. However, there were not any differences between the two intensities used in the urge to smoke. These results are in partial agreement with prior studies which consistently pointed that acute bouts of aerobic exercise significantly lower craving (Bock et al., 1999; J. Daniel et al., 2004; J. Z. Daniel et al., 2006, 2007; Elibero et al., 2011; Everson et al., 2008; Fong et al., 2014; Janse Van Rensburg et al., 2012; Janse Van Rensburg & Taylor, 2008; Kurti & Dallery, 2014; Oh & Taylor, 2014; Prapavessis et al., 2014; Scerbo et al., 2010; M. Ussher et al., 2001; Van Rensburg et al., 2009). Based on the results from this study an intense exercise bout should be followed if decreased urge for smoking is the intention. Given the small degree of methodological differentiations between the present study and those mentioned above, these results are apparently unexpected. This paradox could hypothetically be attributed to the subjective nature of smoking evaluation via answering questions. However, most of the studies supporting a positive relation of exercise with craving reduction used the same 1-7 scale (Tiffany & Drobes, 1991). The exercise duration in most of the above studies was till 15 minutes and the majority of them reported a maximum respective desire-free period. Consequently, an assumption that could explain our results would be that the effect of aerobic exercise on craving has a time limit followed by a recovery period which was incorporated in our 30 minutes programs. Apart from being just a theoretical thought and not supported by research this scenario is quite unlikely as Bock et al. (1999) reported reduced desire after MI and HI exercise lasting till 40 minutes. Another paradox is that despite

changes in desire were not noticed, HI exercise significantly delayed next cigarette smoking compared to control situation and this objective estimation of smoking desire implies that the effect of exercise was not completely neutral. Thus, vigorous aerobic exercise may have a supplementary role in attenuating smoking urge and subsequently in smoking cessation.

Circulating β-E was significantly elevated after both exercise intervention arms compared to pre-exercise which is in line with previous reports (**Table 1**). Interestingly, while all of the above trials indicated an intensity threshold (70% VO_{2max}) to notice significant changes in β-E (Goldfarb et al., 1990; Goldfarb et al., 1991; McMurray et al., 1987; Rahkila et al., 1988), in this trial a moderate intensity (50-60% HRR) was adequate to positively affect β-E. Furthermore, it is not likely that this new finding is attributed to the disparity in intensity estimation methods between the present and the above studies. Despite the fact that %HRR and VO_{2max} are not considered equal anymore (Garber et al., 2011; Hills, Byrne, & Ramage, 1998; Lounana, Campion, Noakes, & Medelli, 2007; Swain & Leutholtz, 1997), Table 2 shows that there are only small declinations between boundary values of each marker and therefore an association between moderate intensity and elevated β-E levels is probable.

In this study the established association between acute exercise and peripheral β-E is strengthened. In addition this is the first study designed to concurrently investigate the impact of acute exercise bouts in smoking urge and hormonal markers which are potentially associated with addiction. However, despite the delay to first cigarette observed after the HI program compared to control, no direct conclusions about smoking craving and β-E can be extracted as urges were not changed in our study. Moreover, there is no available evidence describing the effects of acute exercise on CSF β-E as this interaction remains unknown. Given the physiological integrity of brain β-E system (Veening et al., 2012), post-exercise

peripheral increases are not likely to induce sufficient β-E related reward and substitute nicotine intake resulting in continuous smoking craving.

In line with previous studies (de Meirleir et al., 1986; Farrell et al., 1987; Luger et al., 1987), aerobic exercise of moderate intensity (50-60% HRR) was not enough to alter circulating ACTH levels, whilst the HI program was associated with higher ACTH values in all comparisons performed (versus pre-exercise state, control and MI). Accordingly, the MI program did not significantly affect cortisol levels, supporting previous knowledge that vigorous exercise is required to induce cortisol release (Luger et al., 1987; Pomerleau & Pomerleau, 1990). Nevertheless, since moderate and vigorous exercise had neutral effect on smoking urge in our study, these results cannot provide any direct implications with respect to the involvement of HPA axis hormones in cigarette cravings and the potential role of exercise. This topic has not yet been adequately investigated and the hypothesis that HPA hormones have a causal role in cigarette addiction has not been confirmed or rejected (Richards et al., 2011).

Epinephrine and norepinephrine concentrations reportedly increased following both exercise interventions compared to pre-exercise and control condition. Furthermore, both hormone levels were higher after the HI program versus the MI one indicating an intensity dependent association of acute aerobic exercise and catecholamine release in the blood stream. As mentioned above, basal SNS function in chronic smokers is increased whilst catecholamines' responsiveness to acute nicotine intake is attenuated (Richards et al., 2011). In similarity to the HPA hormones, there is an important gap in literature concerning the potential mediating role of ANS function in addiction and relapse, requiring further research in the future.

6. CONCLUSIONS AND FUTURE DIRECTIONS

This is the first study aimed to assess the effect of acute aerobic exercise, of different intensities, on smoking desire and specific biomarkers (β-E, ACTH, cortisol, catecholamines) on the same group of smokers. In agreement with previous reports by various studies, both moderate and vigorous exercise increased β-E, and catecholamines. Still, the ACTH and cortisol seem to be unaffected by moderate intensity programs.

Deviating from the majority of relevant research, our study did not reveal any significant effect of aerobic exercise on following smoking urge while HI was associated with significant delay to first cigarette compared to the control arm. Results from numerous studies, current opinion is that acute bouts of exercise decrease smoking urge or reduce cravings but this effect has a brief duration and is not preserved beyond 30 minutes. This automatically questions the practical usefulness of acute exercise in smoking cessation, when performed once a day. Therefore, it would be interesting to address the same topic in studies designed to implement multiple exercise programs/day or include both aerobic and resistance models and evaluate smoking urge and the number of cigarettes smoked during the day.

In the physiological approach, the hypothesis that exercise can substitute nicotine-related reward and block reinforcement by increasing β-E warrants further research which will determine the effect of exercise in brain β-E. The implementation of such studies is though limited due to the technical considerations (lumbar puncture).

As mentioned above, the potential causal role of the HPA axis hormones in smoking addiction has to be determined. This could be managed by investigated the isolated effect of these hormones on craving (Richards et al., 2011) to avoid confounding effects. This hypothesis has been assesses in cocaine-dependent individuals showing that stimulation of the axis by CRH infusion can increase cocaine craving (Brady et al., 2009).

In conclusion, our results confirm the effects of acute exercise on HPA axis variables and future studies are needed to enlighten the associations of these markers with smoking urge.

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