

ASSOCIATIONS BETWEEN MELANOCORTIN, DOPAMINE AND SEROTONIN NEUROTRANSMISSION AND PHYSICAL ACTIVITY

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Abstract

Regular physical exercise is beneficial for health. Despite well-known indications to maintain moderate physical activity (PA) throughout the lifetime, recommendations to stay active are disregarded by the majority of people.

Brain neurotransmitter systems influence our motivation and reward. Animal and human studies suggest that dopamine, melanocortin and serotonin may be involved in the regulation of PA. Interesting information has been revealed in association studies on the genes encoding the receptors of the above neuropeptides. Unfortunately, the complexity of interactions with the environment and differences in methods to assess PA do not allow easy conclusions. The area of the molecular basis of our lifestyle is yet to be explored.

Introduction

Far into the 20th century, physical activity (PA) was indispensable for locomotor purposes and necessary for assuring everyday living in most populations. Nowadays, practically all needs can be provided without physical strain. For this reason, spontaneous PA has the greatest impact on the overall level of PA in humans. Unfortunately, the average amount of exercise undertaken by the majority of humans is not sufficient to ensure disease-free living.

In Europe, the sedentary lifestyle ranges between 43% (Sweden) and 88% (Portugal) [1]. In a survey carried out in Poland, more than 50% of men did no leisure-time exercise [2]. Direct costs of low physical activity (and obesity) may reach 9.4% of all health-care system expenses [3].

Health benefits of PA are unquestionable. It is worth underlining that reduced PA appeared to be a strong, independent predictor of all-cause mortality in the Nurses' Health Study (116 564 women followed since 1976) [4], the Cancer Prevention Study II, a prospective cohort of 230 298 women and 90 162 men who were enrolled in 1982 [5] or Finnish cohorts (7925 men and 7977 women followed from 1975) [6,7]. What is especially important, moderate, regular exercise is a preventive measure against epidemics of our time: cardiovascular diseases [8], obesity [9] and diabetes [10].

It has been shown that a high level of PA in subjects aged 50 and more is associated with longer life expectancy and longer living without symptoms of cardiovascular diseases. In this model, moderately ac-

tive (30-33 metabolic equivalents [METs]) and highly active (>33 METs) men could expect to live longer by respectively 1.3 and 3.7 years when compared with men whose PA level was low (<30 METs). Moderately and highly active subjects could also hope for by 1.1 and 3.2 years longer periods without symptoms of cardiovascular disease. The numbers for women were respectively 1.5 and 3.5 years for life expectancy and 1.3 and 3.3 years for living without symptoms of cardiovascular disease [11].

Physical activity together with basal metabolic rate (BMR) and thermic effect of food (TEF) are components of energy expenditure (EE). Physical activity is composed of spontaneous PA (SPA), non-volitional exercise or non-exercise activity thermogenesis (NEAT), obligatory PA, and volitional/voluntary PA (VPA). The first component (SPA or NEAT) comprises activities associated with daily living and the energy spent on activities such as fidgeting, muscle tone, and maintenance of posture. These seem to be particularly difficult to measure in humans. Obligatory PA means locomotor activity needed for survival (which is practically absent in modern populations). Volitional/voluntary PA describes participation in exercise/fitness programmes, individual training, conscious sport and active lifestyle. Among these, spontaneous PA seems to have the greatest impact on overall energy expenditure. In humans it may reach from 100 to 800 kcal/24 h [12,13].

It has been proven that energy expenditure (including PA) is dependent on stimulation of specific areas

of the central nervous system. The hypothalamus plays the key role here as it collects sensory/metabolic stimuli and regulates energy balance. Energy balance is maintained through control of energy intake (food) and energy expenditure (PA, metabolism).

Lesions to specific brain areas have profound effects on PA and, to the contrary, strenuous exercise may influence functions of the central nervous system. For example, physical exercise is a stressor that can activate corticotropin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN). Forced wheel running (FWR) in rats strongly activates CRH neurons in the PVN compared with spontaneous wheel running [14].

Damage made to certain nuclei modifies behaviour and may lead either to hypo- or to hyperactivity. Activity of neurotransmitters is thought to play the key role in these processes. PA of laboratory animals can be either enhanced (e.g. lesions to the cerebral frontal lobe or basal forebrain) or diminished (lesions to the ventromedial hypothalamus, anterior nucleus basalis magnocellularis) [13].

In the case of limited external stimulation for engaging in PA, genetic and metabolic factors that shape PA are a hypothetical target for intervention. But though associations between genes and physical fitness are evident [15,16], the actual role of genes for adherence to a physically active lifestyle has not been fully elucidated [17-19].

We concisely summarize information on inheritance of features associated with PA. Additionally, we discuss the importance of brain neuropeptides for human behaviour, as a range of observations suggest that physical activity is dependent on the intact brain dopamine, serotonin and melanocortin signalling.

Genetic mechanisms regulating PA

Animals

Data on molecular determinants of physically active lifestyle have been growing in recent years. Animal studies revealed loci for locomotor activity in insects and rodents [20-22]. In the fruit fly, genes encoding cGMP-dependent protein kinase decide on more or less active behaviour (in regard to food searching) [20]. It has been shown that closely related mice strains have similar PA levels. Mice bred selectively for high wheel running, even after 35 generations, ran 170% more than controls [23]. Autosomal recessive gene defects as in *ob/ob* mice (leptin is not produced in adipose tissue) result in decreased PA [12].

Humans

Genetic linkage studies investigate correlations between inheritance of a trait and genetic material within family units (siblings, multigeneration families). It is obvious that the importance of genes for a given fea-

ture should be confirmed by revealing resemblances of phenotypes in related persons. The best material for such studies are monozygotic twins that carry the same genotype. All the phenotypic variance in monozygotic twins is dependent on the environmental influences only. The genotype of dizygotic twins of the same gender is 50% identical. Resemblance of phenotypic features whose expression is highly dependent on genotype in dizygotic twins is significantly lower than in monozygotic twins.

It is common knowledge that some individuals are intrinsically keen on participating in exercise and others not. It may be observed in childhood, but becomes evident in older years. On the other hand, there is no doubt that the environment to which an individual is exposed may override genetic predispositions.

Most twin or family studies show a considerable influence of the genetic component on physically active phenotype/lifestyle [24,25]. In some estimates heritability coefficients for sport participation are between 0.35 and 0.83 and for daily PA between 0.29 and 0.62 [26].

Canadian authors aimed at distinguishing between genetic and cultural components influencing the level of habitual PA in the transmissible effect between generations. They questioned 1610 subjects from 375 families on the level of their habitual PA (3-day activity record 1978-1981). Familial correlations were computed after adjustments for the effects of age, sex, physical fitness, body mass index, and socioeconomic status, and analysed with a model of path analysis that allows the separation of the transmissible effect between generations into genetic and cultural components of inheritance. It was concluded that PA was determined mainly by non-transmissible, environmental factors, but genes affected the level of habitual PA in 29% [27].

An American study of 3344 male twins (aged 33-51) revealed a clear, familial aggregation in PA (with odds ratio from 2.9-4.6 and 1.4-1.9 for intense and moderate activities, $P < 0.05$) [28]. In a study of 117 monozygotic twins aged 35-69, familial aggregation accounted for 43% of exercise variation in adulthood [29]. In the Quebec Family Study, heritability estimates for the degree of inactivity, moderate to strenuous PA, total level of daily activity and time spent on PA in the past year were respectively 25%, 16%, 19% and 17% [30].

On the other hand, 24-hour energy expenditure measured in respiratory chambers of 71 siblings from 32 different families (Caucasian) showed that the variance among subjects was related mainly to fat-free mass (82%) and, to a lesser extent (10%), to spontaneous PA, fat mass, serum free triiodothyronine (FT3) and norepinephrine. Family aggregation of energy expenditure was suggested to be related to resemblance of body composition mainly (and not to spontaneous PA) [31].

An invaluable source of information on associations/linkage between genotype and PA in humans is the Human Gene Map for Performance and Health-Related Fitness Phenotypes (published annually, with updates from 2000) [32]. In the 2005 update, the authors mentioned 165 autosomal loci/QTL and 5 on the X chromosome. Moreover, variants of 17 mitochondrial genes were found to be associated with fitness or performance phenotypes [33]. The newest report was published in 2010 [16]. Among other known causes, alterations of neurotransmitter systems have a high potency to influence locomotor activity [34].

Dopamine

The central dopaminergic system influences learning, motivation, reward, reinforcing mechanisms and addiction. The dopaminergic system regulates movement of both animals and humans. It is worth mentioning that interactions between PA and the dopaminergic system are reciprocal and exercise modifies production and actions of brain dopamine. On the other hand, dopamine signalling modulates effects of other neurotransmitters that are involved in the control of motor activity [35].

Dopamine exerts its actions through five receptors, D1-D5 (DRD1-DRD5), which are present in nearly all areas of the brain. DRD1 and DRD5 activate adenylyl cyclase and increase cAMP production. DRD2, DRD3 and DRD4 exert opposite effects and decrease cAMP production through inhibition of adenylyl cyclase activity. The above-mentioned effects are mediated by Gi-proteins [23].

The importance of dopamine in motor movement control is easiest to investigate in clinical conditions such as Parkinson's disease, ADHD (attention deficit hyperactivity disorder) or depression. Parkinson's disease comprises a range of problems such as muscular rigidity, resting tremor, difficulty with movement initiation (bradykinesia), slowness of voluntary movement, difficulty with balance and difficulty with walking. The underlying cause of the disease is loss of dopaminergic neurons in the substantia nigra of the basal ganglia. In patients with ADHD, hyperactivity derives from disturbances in dopamine signalling. Methylphenidate inhibits the reuptake of dopamine and is effective in controlling symptoms in 60-70% of ADHD patients. It has been found e.g. that specific genotypes of DRD4 and DRD5 are associated with increased risk of ADHD [36]. It is also known that patients with depressive syndromes (low dopamine levels) benefit from regular exercise [37].

In experimental models, an increased level of dopamine within the midbrain stimulated locomotion [38], while a low level of dopamine resulted in hypoactivity [39].

In mice a positive relationship was observed between DRD2 deficiency and reduced locomotor activ-

ity [40]. There are also convincing data indicating an association between *DRD1* and PA [41]. Expression of *DRD1* was lower in high active as compared with low active mice [42]. Application of an antagonist of D1 receptors decreased the level of voluntary PA in mice bred for high wheel running [43]. Another study showed that selectively bred mice had higher expression of dopamine receptors DRD2 and DRD4 in the hippocampus than control lines [44].

Just recently there has been proposed a model of the central regulation of PA in which the dopamine system plays the key role [23]. According to this model, low expression or impaired function of DRD1 and DRD5 increases the level of PA (through reduced inhibitory signalling), while high expression and intact function of DRD2, DRD3 and DRD4 have inhibitory effects on PA (through increased stimulatory transmission). At the same time, PA increases dopamine production and signalling.

Animal observations on the role of dopamine for locomotor activity were confirmed in human familial cohorts in the Quebec Family Study. There has been found an association between dopamine D2 receptor gene (*DRD2*) polymorphism and PA levels among white women. Heterozygotes or homozygotes C/C were more active than homozygotes T/T when evaluated by a questionnaire recalling PA in the previous year. However, no association was found in men or black women [45]. Such findings are especially intriguing when one remembers that age-related deterioration in PA is – at least in part – dependent on the dopaminergic system [46]. We could not prove the above-mentioned speculations in our own material (results in press).

Melanocortin

The melanocortins (melanocyte-stimulating hormones, MSHs) are peptides that derive from proopiomelanocortin (POMC). POMC comprises three domains that contain forms of MSH: pro- γ -MSH, ACTH and β -lipotropin. MSHs exert their effects through five receptors (MC1-MC5). α -MSH and agouti-related protein (AgRP) are respectively an agonist and an antagonist of the brain melanocortin receptors [47,48]. MSHs influence a wide range of body functions: nervous, endocrine, immune and behavioural. MSHs stay in functional balance with opioids and are implicated as mediators of the central effects of leptin. MSHs have a prolonged, inhibitory effect on feeding in rodents and humans. Reduced activity of the CNS melanocortin system promotes reduced locomotor activity.

The status of CNS MC4R has been shown to influence the energy balance through direct effects on autonomic outflow and metabolism [49]. Expression of MC4R is especially high in the hypothalamus and the spinal cord.

Interruption of the melanocortin signalling in the hypothalamus leads to reduced PA and obesity in mice. Male non-obese MC4R knockout mice are less physically active than wild-type controls [50]. At the same time, administration of an antagonist of MC4R reduces spontaneous locomotor activity of rats [47].

Stimulation of MC4R increases PA/energy expenditure and leads to weight loss [51], while MC4R deficiency is the most common genetic cause of obesity [52].

Val103Ile is the most frequent polymorphism of MC4R that is linked with obesity [53,54]. In one study, subjects with the Val103Ile variant of the MC4R gene had higher energy expenditure than ones with the Val103Val variant. After a 3.5-year follow-up of a subgroup aged 70 ± 3 years (BMI 27.4 ± 4), subjects with 103Ile genotype gained weight whereas subjects with Val103Val genotype lost weight [55]. The authors of another investigation found that a relatively infrequent G/A genotype of the Val103Ile MC4R polymorphism was negatively associated with average weight [56]. It has been hypothesized that the Val103Ile polymorphism may be related to PA and parameters of the metabolic syndrome [57].

Lower levels of moderate/high PA and sedentary lifestyle were found in the T/T variant of the C-2745T polymorphism of MC4R gene. In a family study, T/T homozygous offspring (but not parents) had a lower level of PA and lower BMI than other variants. It was suggested that the T/T genotype could result in a weight gain in older years. The authors of the investigation pointed to the fact that T/T homozygotes were least physically active if they were concomitantly A/A homozygotes for the CART-A1475G variant. In turn they were most physically active if they carried the G allele of the CART-A1475G variant [58].

In our investigation performed in a sample of Polish men, there was no statistically significant association between the MC4R C-2745T polymorphism and the level of PA [59]. T/T homozygotes led a more sedentary lifestyle and tended to be less physically active, but only in subgroups reporting a low or moderate amount of physical effort undertaken daily (these differences did not reach statistical significance).

Serotonin

The serotonergic system plays an important role in human behaviour. Serotonin (5-HT) is a mediator in emotional disorders: depression, suicide, impulsive behaviour and aggression. It also affects temperature regulation, sensory perception and mood control. Many of these areas are controlled in concert with the central dopaminergic system. It is highly probable that effects of serotonin on locomotion are dependent on secondary effects on other neurotransmitter systems [34].

Acute exercise induces serotonin biosynthesis and release of brain serotonin [60]. Animal studies suggest that interventions within the brain serotonergic system affect motor control and locomotion. However, these relations are not elucidated yet. In an experimental model, dopamine transporter gene knockout mice displayed high levels of PA. Surprisingly, this feature could be attenuated by administration of selective 5-HT transporter inhibitor (fluoxetine) or 5-HT enhancers (5-hydroxytryptophan or L-tryptophan) [61].

The authors of another study showed that injecting an antagonist of the 5-HT_{1B} receptor (RU 24969) into the substantia nigra of a rat causes rotary movements of the animal [62]. It was also reported that stimulation of the 5-HT_{1B} receptor with an active antagonist (CP 94253) may increase the locomotor activity of laboratory animals [63].

Our group has not observed relationships between the G861C polymorphism of the 5-HT_{1B} serotonin receptor gene and the activity level in healthy men. However, in subjects presenting the lowest level of PA, the distribution of genotypes was different to that expected by the Hardy-Weinberg equilibrium [64].

It was hypothesized that deteriorating (after initial good effects) results of ADHD treatment with inhibitors of dopamine and noradrenaline reuptake indicate a role of 5-HT in these mechanisms [65]. Serotonin, as well as dopamine, is supposed to increase PA in anorexia nervosa [23]. On the other hand, exercise modulates serotonin signalling [35]. However, to the best of our knowledge, there is no clear evidence that PA can modify serotonin or dopamine systems in such a way to prevent their age-related decline.

Conclusions

Increasing the level of PA remains the key target in the majority of health interventions. Unfortunately, effective tools to achieve this goal are still lacking.

Secretion and signalling within the central dopamine, serotonin and melanocortin systems reveal many interesting associations with locomotion and a propensity to be active. Animal observations offer promising areas for molecular investigation, though these models cannot be simply transferred to humans.

It is tempting to hypothesize that we could 'dose' and 'adjust' physical activity according to the genetic characteristics of a subject. Eg. carriers of BRCA1/BRCA2 mutations are advised to undergo preventive mastectomy to avoid the development of breast cancer. Maybe efforts to maintain/increase the level of physical activity could be focused on subjects distinguished upon genetic examination? Newer methods allow scanning of the entire genome for associations with behavioural traits. Unfortunately, such an approach is not yet applicable to specific individuals in the foreseeable future.

Declaration of interest

The authors report no conflicts of interest.

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