Mini Review

Translational Science: how experimental research has contributed to the understanding of spontaneous Physical Activity and Energy Homeostasis

Izabelle D Benfato
Thaís L Moretto
Marcela Barthichoto
Francine P de Carvalho
Camila A M de Oliveira

Universidade Federal de São Paulo, Santos, SP, Brasil

Abstract — Spontaneous physical activity (SPA) consists of all daily living activities other than volitional exercise (e.g. sports and fitness-related activities). SPA is an important component of energy expenditure and may protect from overweight and obesity. Little is known about the biological regulation of SPA, but animal research has contributed significantly to expand our knowledge in this field. Studies in rodents have shown that SPA is influenced by nutrients and volitional exercise. High-fat diet seems to decrease SPA, which contributes to weight gain. Volitional exercise may also reduce SPA, helping to explain the commonly reported low efficiency of exercise to cause weight loss, and highlighting the need to find a volume/intensity of exercise to maximize total daily energy expenditure. Animal studies have also allowed for the identification of some brain areas and chemical mediators involved in SPA regulation. These discoveries could enable the development of new therapeutics aiming to enhance SPA.

Keywords: energy balance, free-living activity, volitional exercise, sedentary behavior.

Introduction

Lack of physical activity contributes to the disruption of energy homeostasis, favoring a positive energy balance. Chronically, the result is overweight and obesity. Thus, in the current scenario of obesity epidemic, it is not surprising the alarming numbers regarding inactivity. In 2012, worldwide, 31.1% of adults were considered physically inactive, with proportions ranging from 17.0% in south East Asia to about 43% in the Americas and the eastern Mediterranean.

This panorama can be explained by the increase in time spent in sedentary behaviors (activities with very low energy expenditure, such as TV viewing, computer and game-console use in the sitting position, workplace sitting, and time spent in automobiles) at workplace, at leisure, at home and transport, over decades. An assessment from the National Health and Nutrition Examination Survey in the United States 2003–2004 revealed that many adults spend 70% or more of their waking hours sitting, 30% in light activities and little or no time in exercise.

Sitting time is positively associated with increased risk for cardiovascular disease and all-cause mortality. Notably, even for those meeting the public-health guidelines on physical activity, sitting for prolonged periods is associated with adverse outcomes. Thus, it is clear the health benefits one can obtain by reducing the time spent on sedentary behavior, even if performing moderate to vigorous physical activities. This highlights the importance of low-intensity physical activity, whose contribution to either health or to total daily energy expenditure is usually neglected.

Whereas it is estimated that physical inactivity is responsible for 6% of cases of coronary artery disease, 7% of cases of type 2 diabetes mellitus and 10% of breast and colon cancers, strong evidence indicates that reducing physical inactivity by 10% to 25% could avoid 533,000 to 3 million deaths per year, respectively. Besides, high levels of physical activity are associated with a gradual increase in life expectancy.

Environmental (e.g. drive-through, city architecture) and socioeconomic (e.g. violence, lack of opportunity for leisure) factors are some of the elements known to affect physical activity negatively. The biological aspects, however, remain poorly understood. In this review we discuss the contributions of animal studies to the understanding of the biological determinants of spontaneous physical activity, which encompasses all forms of activities other than volitional exercise (e.g. sports and fitness-related activities), and its impact on energy homeostasis.

Components of Energy Homeostasis

To be in a neutral energy balance, or to achieve energy homeostasis, energy intake and expenditure must be also in balance. As shown in Figure 1, in humans and rodents energy expenditure includes basal metabolic rate (BMR), the thermic effect of food (TEF), and activity thermogenesis (AT). BMR is the...
energy expended when an individual is laying down at rest in the postabsorptive state, and corresponds to about 60% to 70% of total daily energy expenditure, or TDEE\(^{12}\). BMR can be affected by either resistance or endurance training. As non-fat mass is a major factor in determining basal metabolic rate\(^{13}\), the increase in muscle mass as a result of resistance training can consequently increase BMR. With respect to endurance exercise, it has been shown to increase the production of the thermogenic myokine irisin, which drives the browning of white fat\(^{14}\). The energy spent for digestion, absorption and processing of food, or TEF, varies between 5% and 15% of TDEE. Finally, activity thermogenesis is the energy used for spontaneous muscle contractions, body movements (physical activity), and is the component of energy expenditure which varies the most\(^{12}\). Thermoregulation is not depicted in Figure 1, as people wear appropriate clothes and so the energy expended to maintain body temperature is neglected. Rodents, however, are maintained in animal facilities at temperatures below their thermoneutral zone (21°C), implicating a substantial cost of thermoregulation\(^{10}\).

Physical activity can be subdivided into volitional exercise (VE) and spontaneous physical activity (SPA). Whereas volitional exercise is all kind of exercise done in a systematic way (e.g. sports and fitness-related activity), SPA refers to activities other than VE, such as daily living activities, yard work, fidgeting, posture maintenance, and non-specific ambulatory behavior\(^{15}\). The energy spent only in SPA is called non-exercise activity thermogenesis (NEAT), and for those individuals not engaged in any form of volitional exercise, NEAT is the sole responsible for AT. NEAT can vary from 100 kcal to 800 kcal/day in very active individuals\(^{15,16}\), and the importance of NEAT for energy homeostasis has been demonstrated in studies with humans\(^{17}\) and rodents\(^{18,19}\).

For rodents, SPA refers to all form of activities including ambulatory and non-ambulatory behavior\(^{16}\). Caution is needed regarding wheel running, which is commonly used as a model of volitional exercise and is not equivalent to SPA, as it engages different neural and physiological mechanisms\(^{15,20}\). Swimming\(^{21,22}\) and treadmill running\(^{23}\) are also commonly used as an equivalent form of volitional exercise in rodents.

### Nutrients, Energy Intake, and Spontaneous Physical Activity

Feeding influences energy homeostasis primarily due to its effect on energy intake. However, nutrients and the caloric content of the diet can also affect SPA and, consequently, energy expenditure\(^{24,25}\). As diet modification, both in terms of calorie density and also macronutrients, is a common tool to promote body weight loss, a more comprehensive view of how diet-changing can affect total daily energy expenditure is of great importance. The contributions from animal studies to this field are discussed below.

### High-fat diet

The deleterious peripheral and central effects of high-fat diet are well established\(^{26,27}\). Interestingly, high-fat diet has also been shown to decrease spontaneous physical activity in rodents\(^{18,24}\). This effect could be seen as early as after a few hours on the diet, and it remained throughout the 21 days in which mice received the diet rich in fat\(^{18}\). According to the authors, the reduction of locomotor activity had an essential role in weight gain and obesity. They found that the energy intake and the energy absorbed were higher in high-fat than in standard-diet fed mice only in the first 24 hours, whereas body weight and fat gain increased all over\(^{18}\).

### Low-protein diet

Perhaps for methodological issues\(^{15,20}\), studies associating low-protein diet and locomotor activity are still scarce and controversial. Rats suckling in large litters and therefore with limited access to food after weaning. Similarly, rats whose mothers were fed a low-protein diet during pregnancy and lactation (5% protein) were also more active\(^{28}\). However, Duran et al.\(^{29}\) found no alterations in overall activity level (measured by radiotelemetry) in rats with a history of protein malnutrition. They observed, instead, alterations in the pattern of locomotor activity\(^{29}\).

### High-protein diet

Yamaoka et al.\(^{30}\) found that male Sprague-Dawley rats fed a high-protein, carbohydrate-free diet decreased locomotor activity but had increased body temperature and reduced body weight when compared to male rats fed with a normal-protein diet. Differently, Oishi et al.\(^{31}\) found no differences on locomotor activity and body temperature in mice receiving a low-carbohydrate high-protein diet. Thus, whether the protein content of the diet modulates spontaneous physical activity remains to be determined.
Calorie restriction

Calorie restriction affects SPA differently depending on factors such as severity, duration of food deprivation, and species. In Wistar rats, whereas moderate (30%) feed restriction did not change SPA, severe (approximately 80%) restriction reduced spontaneous activity, resulting in energetic economy. In another study, chronic caloric restriction (CR) increased SPA during the time interval preceding anticipation of food in obesity-prone and Sprague-Dawley rats, but not in obesity-resistant rats, which already have elevated basal SPA. Brzek et al. investigated the effect of a moderate CR on SPA in mice divergently selected for high or low basal metabolic rate. CR increased total SPA and SPA intensity in both lines, but the latter increased more in the group selected for low basal metabolic rate. Mice selected for high basal metabolic rate have increased basal SPA, and maintained their genetically determined high SPA even under CR. In general, CR results in an acute increase in activity, whereas severe restriction decreases SPA, which then conserves energy. However, there is considerable influence of the genetic background.

Volitional Exercise and Spontaneous Physical Activity

Volitional exercise is one of the most used tools to induce negative energy balance and weight loss. However, not rarely, the results are disappointing and the observed body weight reduction is less than predicted. Besides the well-known increase in energy intake, volitional exercise can interfere negatively with SPA, and these compensatory behaviors may minimize the exercise efficiency to reduce body weight. Copes et al. found that daily free access to a running wheel, a form of volitional exercise in rodents, decreased SPA. In the same line we found that both lean and diet-induced obese mice, which had free access to running wheels 5 days per week, had reduced SPA in the resting days. As wheel running does not allow for the control of volume and intensity, the exercise load might have been inappropriate, triggering a compensatory decrease in SPA. Interestingly, when aerobic swimming exercise at individualized intensity was used, it avoided the decline in SPA observed in non-trained rats after 12 weeks. Thus, an adequate amount/intensity of volitional exercise should be established so that SPA could either be kept at a constant level or even increased. As every body movement has its associated energy cost, increasing volitional exercise but reducing SPA could result in no change in total daily energy expenditure (Fig. 2). In our study, as a result of both increased caloric intake and decreased SPA, wheel running failed to decrease body weight in lean and obese mice. Accordingly, Morio et al. found that a progressive endurance training in elderly individuals did not change their total daily energy expenditure due to a compensatory decrease in free-living activities. On the other hand, Rosenkilde et al. showed that moderate exercise accumulated a negative balance 80% greater than expected, without increasing energy intake. They speculate this greater-than-expected energy expenditure could have been caused by an increase in SPA. In sharp contrast, the group performing the higher-dose exercise accumulated a negative balance 20% less effective than expected.

Thus, it is clear that when exercise is used as a tool to promote negative energy balance, the compensatory behavior it triggers must be taken into account. Besides the increase in energy intake, a decrease in SPA might compromise the successful use of exercise as a mean to induce body weight loss. In this context, animal studies provide a unique opportunity to investigate how SPA is regulated, what are the mechanisms involved in compensation, and how to avoid SPA decline. We believe a better understanding of SPA can impact directly exercise programs aiming for weight loss, contributing to the fight against obesity.

Aging and Spontaneous Physical Activity

Aging is a process marked by several metabolic and physical changes. These changes, associated with the sedentary behavior characteristic of the aging process, make older people more susceptible to chronic diseases. There is a clear age-related decrease in SPA and energy expenditure. Additionally, elderly people seem to be especially susceptible to compensation in SPA caused by volitional exercise. Poehlman observed a 62% reduction in NEAT after voluntary exercise in older people. As a consequence, total daily energy expenditure did not change despite volitional exercise. Similar results were found by Morio et al.

The understanding of the mechanisms involved in the reduction of SPA during aging, including the apparently higher susceptibility to volitional exercise-induced decrease in SPA, could enable the adoption of strategies at critical periods of life to combat sedentary lifestyle and the associated comorbidities. In this scenario, rodent models are sorely needed due to their relatively short lifespan. As an example, mice are considered middle-aged when 40 weeks old and senescent when 72 weeks old, making studies on aging much more viable in rodents than in humans. Some advances have already been achieved, such as the role of hypothalamic neuropeptides on the decrease of SPA, as discussed in the next session.
Central Regulation of Spontaneous Physical Activity

Although it is not clear how SPA is regulated, due to animal studies some areas within the central nervous system (CNS), as well as some neuropeptides and hormones, are emerging as candidates. One of the CNS regions is the hypothalamus, more specifically the arcuate nucleus (ARC). ARC is known to play an essential role in energy balance, connecting afferent signals with central circuits, and transmitting efferent commands to control food intake, locomotor activity, and peripheral cell metabolism. In addition to the hypothalamus, there are other regions in the CNS which seem to regulate SPA and NEAT, which include: the mesencephalic locomotor region, locus coeruleus (LC), ventral tegmental area (VTA), substantia nigra (SN), tuberomammillary nuclei (TMN), pedunculopontine and laterodorsal tegmental nuclei, nucleus accumbens (NAcc), and striatum.

NPY, a neuropeptide expressed mainly in a subtype of neurons in ARC, was recently shown to increase SPA. Intracerebroventricular (i.c.v.) administration of NPY resulted in a shift of metabolism towards lipid storage and an increased use of carbohydrates, while at the same time increasing locomotor activity, energy expenditure, and body temperature. Pfluger et al. observed the same increase of SPA following NPY i.c.v. administration. On the other hand, AgRP i.c.v. administration resulted in a significant decrease of SPA and increased food intake.

Orexin A (hypocretin), another neuropeptide, has also been shown to be involved in the central regulation of SPA. Orexin neurons are concentrated in the lateral hypothalamus (LH), perifornical area, and dorsomedial hypothalamus. Some studies in rodents suggest the effect of orexin A on SPA is more relevant to energy balance than its role on the control of food intake. Orexin A infusion in LC promotes SPA but not food intake, suggesting its signaling in LC promotes negative energy balance and reduction of adiposity. In another study by Teske et al., it was shown that orexin projections from the LH stimulates orexin and dopamine signaling in the SN and promotes SPA. Importantly, a reduced activity of hypothalamic orexin signaling seems to be related to the decrease in spontaneous physical activity during aging.

In relation to hormones, insulin and leptin emerge as potential modulators of SPA. Henige et al. showed that insulin i.c.v. injection promotes SPA in lean but not in diet-induced obese mice, which develop hypothalamic resistance to insulin. In addition, the pharmacological inhibition of insulin signaling in hypothalamus also decreased the locomotor activity in mice. With respect to leptin, the positive association between this hormone and physical activity in rodents was first shown by Pelleymounter et al. Over the years, other studies have demonstrated the effect of leptin in increasing locomotor activity. In humans, however, the results are contradictory. Belcher et al. observed that high levels of leptin preceded a fall in the levels of physical activity in female children with obesity risk. A negative correlation between leptin levels and physical activity in healthy girls, independent of puberty stage and adiposity, has also been observed. However, the same correlation was not observed in healthy boys.

Besides the hormones and neuropeptides mentioned, there are other molecules which may be involved in the regulation of SPA, including cholecystokinin (CCK), corticotropin-releasing hormone (CRH), neuregulin U (NMFU), and ghrelin. The role of brain-derived neurotrophic factor (BDNF) in stimulating locomotor activity has also been demonstrated.

Conclusion

The worryingly high number of inactive individuals together with data showing that physical inactivity is more fatal than obesity per se make evident the urge of approaches to stimulate SPA. Animal studies have allowed some important advances in our understanding of the neuroendocrine mechanisms modulating SPA and how SPA can be affected by factors such as nutrients, volitional exercise, and aging. This knowledge can have implications for the development of new pharmacological and non-pharmacological strategies (diet and volitional exercise) to combat sedentary behavior, obesity, and the associated co- morbidities. Additional studies are needed to further elucidate the biological regulation of SPA.

References

10. Garland T, Schutz H, Chappell MA, Keeney BK, Meek TH, Copes LE, et al. The biological control of voluntary exercise,