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EDITORIAL

Is sildenafil a doping drug in hypoxic conditions?

Phosphodiesterase type 5 (PDE5) inhibitors are the first line medicaments recommended for erectile disfunction (ED) [1]. First, sildenafil was marketed in 1998, followed by vardenafil and tadalafil in 2003. More recently, in 2012 the second generation avanafil was approved by Food and Drug Administration (FDA) [2]. As concern their mechanism of action, PDE5i interfere with the cGMP (guanosine 3′,5′- monophosphate) signalling pathway. *via* the inhibition of phosphodiesterase type 5, they hamper the hydrolysis of the second messenger cGMP. Hence, the accumulation of high concentration of cGMP triggers a cascade of cellular events, as well as the activation of a protein kinase G (PKG), responsible for a lowering of the intracellular Ca^{2+}, that determines the relaxation of smooth muscle and the penile erection [3]. Phosphodiesterase (PDE) superfamily consists of 11 different isoenzymes. Due to their different allocation thought the body and substrate specificity, these isoenzymes are involved in the regulation of different physiological processes [4,5]. PDE5 selectively binds cGMP and is mainly distributed at the smooth muscle of the corpus cavernosum, but it was also detected in skeletal muscle, vascular, airway, platelets and visceral smooth muscle [6]. Current data showed that, apart from type 5 PDE isoform, PDE5 interacted with other PDE isoforms, that are responsible for their side effects [7]. Due to the central role in the regulation of different physiological process *via* cGMP signalling pathway, PDE5 seems to be an attractive target for novel therapeutical applications. Currently, PDE5 inhibitors were approved for the treatment of pulmonary arterial hypertension (PAH) and lower urinary tract symptoms (LUTS) [8,9]. There is also well-documented evidence that these PDE5 inhibitors should act as effective ergogenic aid agents for exercise or sport in condition of moderate or severe hypoxia [10]. This editorial will focus on the potential actions of Sildenafil on physical activity in hypoxic conditions, an aspect neglected in the literature and not considered in sports clinical practice. We choose to focus our study on Sildenafil because there is little or no evidence regarding Tadalafil, Vardenafil and Avanafil; in particular with the following search strategy: tadalafil or vardenafil or avanafil AND physical activity AND hypoxia we find only two items. Tables 1–3 provide data on Sildenafil impact with respect to physical activity and metbolism.

Analyzing the data, Olfert et al. assumed that in hypoxia condition the vasodilatory effect of sildenafil led to an augment of arterial PO_2 and O_2 saturation, as well as the pulmonary gas exchange during exercise, resulting in an improvement of physical performance. Following the sildenafil administration, the increase of pulmonary capillary blood flow ameliorated the reduction in arterial oxygen saturation under hypoxia conditions [11]. Furthermore, in the same study sildenafil intake resulted also in an increase of hearth rate at rest [11]. Similar effect on cardiac functions was obtained by Ghofrani et al. [10]. Data showed that in healthy mountaineers and trekkers exposed at 5245 m in Mount Everest camp the consumption of 50 mg of sildenafil was associated to a decrease of pulmonary arterial pressure (PAP) (19%) at rest and during exercise (18%) [10]. The favourable effects of sildenafil on exercise performance were also evaluated by Ricart et al. Here, the treatment with sildenafil (100 mg) in 14 healthy volunteers caused a notable increase of heart rate during exposure to hypobaric hypoxia (5000 m of simulated altitude) at rest and following exercise. No noteworthy differences in systolic PAP, in normoxia condition either at rest or during exercise, were appreciated. However, data on ventilatory parameters were inconclusive to support the aim of the study [12]. By contrast Salinas et al. failed to find a beneficial effect of sildenafil on exercise performance in normoxia and hypoxia conditions at rest and during maximal and submaximal intensity of exercise [13]. No one among 11 healthy young volunteers involved in this study experienced an improvement in SaO_2 following sildenafil intake in hypoxia conditions [13]. This finding was in line with the study by Jacobs et al. that demonstrated that sildenafil did not affect cardiovascular hemodynamic and SaO_2 and no favourable effect on physical fitness capacity at a simulated high altitude (∼3900 m) was seen [14]. This data discrepancy might be attributed to different experimental parameters used in these studies, including the intensity of the exercise (maximal or submaximal intensity) and threshold and duration of hypoxia applied [13]. Hypobaric normoxia and hypoxia conditions lead to different physiological states. In hypobaric hypoxia the reduction of barometric pressure provokes a greater dead space ventilation that results in higher values of hypoxemia, hypocapnia, blood alkalosis and lower levels of blood SaO_2 [15]. Also, long-term or short-term administration of sildenafil can differently affect the performance outcome. According to Faorio et al. acute administration of sildenafil in hypoxia impacted positively the physical capacity (higher levels of SaO_2 and gas exchange at altitude), however the drug failed in modifying maximum VO_2 or O_2 saturation in chronic hypoxic conditions [16]. By contrast, other data by Richalet et al.

Table 1. Summary of studies supporting enhancing function on physical exercise of Sildenafil.

Study authors	Intervention	Findings	Conditions	References
Olfert et al.	Sildenafil	↑arterial PO2 ↑ SpO2 ↑Pulmonary gases exchange ↑pulmonary blood flow ↑heart rate	Hypoxia conditions	[11]
Ghofrani et al.	Sildenafil 50 mg	↓ PAP (at rest and during exercise)	–	[10]
Ricart et al.	Sildenafil 100 mg	↑ heart rate (at rest and during exercise) ↔PAP	Hypobaric hypoxia	[12]
Faorio et al.	Sildenafil	↑SpO2 ↑Pulmonary gases exchange	Hypoxya	[16]
Richalet et al.	Sildenafil 120 mg	↑PaO2 ↑ Heart rate ↑ Caridac output	–	[17]

Table 2. Summary of studies which didn't find a beneficial effect of Sildenafil on physical activity.

Study autors	Intervention	Findings	Conditions	References
Salinas et al.	Sildenafil	↔Exercise performance ↔SpO2	Normoxia and hypoxia	[13]
Jacobs et al.	Sildenafil	No influence on cardiovascular hemodinaic No favourable effect on physical fitness ↔SpO2	–	[14]

Table 3. Summary of experimental studies on metabolic modification induced by Sildenafil.

Study autors	Model	Intervention	Organ	Effects	References
Sheffield-Moore et al. Balon et al.	Man	Sildenafil	Skeletal muscle	↑Proteins synthesis ↑Glucose uptake ↓Muscle fatigue	[19,20]
Kobayashi et al.	Mouse	Sildenafil	Muscle	Improvement of function after exercise	[25]
Kim et al.	Rats	Sildenafil	Muscle	↑Endurance of performance	[26]

found that longer intake of sildenafil (3×40 mg/day for 6 days) at 4,350 m resulted in greater PaO_2, heart rate and cardiac output at rest and during exercise [17]. Likewise, Hsu et al. corroborated the positive effects of sildenafil on exercise capacity and experimental time trial at simulated high altitude but not at sea level. It is interesting that a response variability to treatment with sildenafil was found among the treated individuals, defined for this reason as sildenafil "responders" and "nonresponders", demonstrating that only some among trained subjects took advantage from using sildenafil in acute hypoxia [18].

It was also supposed a putative effect of sildenafil at level of skeletal muscle, where it seems to be involved in the stimulation of protein synthesis, reduction of muscle fatigue as well as the increase the uptake of glucose [19,20]. Furthermore, sildenafil was proven to have the same efficacy of testosterone in the stimulating the skeletal muscle protein synthesis [19,21–23]. According to Percival et al. neural NOS (nNOs) regulates contraction-induced fatigue in trained skeletal muscle mouse, while nNOS-deficient muscles showed abnormal hypertrophic growth, weakness, excessive fatigue, slow recovery after physical activity [24]. In mouse model with muscular dystrophy the acute intake of phosphodiesterase 5 inhibitors resulted in an improvement of muscle functions after exercise due to the improved muscle perfusion [25]. Sildenafil citrate also ameliorated the endurance of performance acting on peripheral fatigue in rats [26].

Hence, taken together these findings allow to assume that in altitude or hypoxia conditions Sildenafil, should act as performance enhancers during sport or exercise and doping substances when positively affect the physical capacity in athletes and mountaineers [13]. However, according to literature, an in-dept analysis of the effects of these drugs is required to solve some following points: the experimental conditions (threshold altitude and intensity of exercise to apply to the exposed subjects) at which these inhibitors will be effective in improving exercise performances and mountain activities; the side effects; predictive factors for "responders" subjects; long-term effects of drug therapy for acute mountain illness [13,18].

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