Original Article

Influence of Physical Activity and Olfactory System on Coagulation Factors in Rats

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Abstract

This study was designed to determine the effects of physical activity and olfactory bulb on coagulation factors in rats. Male Wistar rats (n=60) weighing 90-100 gr were divided into 2 groups; experimental group (olfactory bulbectomy) and control group (without olfactory bulbectomy). In each group, animals were divided into 3 subgroups: short-time (5 minutes of physical activity), long-time (with 20 minutes of physical activity), and control (without physical activity), Blood samples were collected from the rat tail tip to determine the coagulation time. Exercise programs included swimming on the water pool until five minutes (short-time) and twenty minutes (long-time) in the experimental groups. The autopsy was performed on all rats and thrombin time was measured for each of the tissues. The results demonstrated that shot-time physical activity significantly reduced thrombin time on tissues of rats compared to the baseline values in the control group (P<0.001). In contrast, a long-time physical activity significantly increased thrombin time in various tissues in olfactory bulbectomy rats (P<0.001). Moreover, our results proved that in olfactory bulbectomy rats after a long-time physical activity, coagulation time increased but after a short time one, it decreased. In conclusion, these results suggest that there is a functional relationship between exercise and olfactory bulb and changes of hemostatic parameters in blood and regulation of circadian rhythms.

Keywords: Thrombin time, Coagulation factor, Coagulation time, Physical activity, Exercise, olfactory bulb, Rat

Introduction

The olfactory system plays an important role in the health and behavior of mammalians. Smell dysfunction significantly influences everyday safety, nutritional status, quality of life, as well as physical well-being and has a relationship with increased mortality [1, 2]. The findings of Corthell proved that melatonin receptors are present in the olfactory bulb and may affect olfactory function. In addition, they showed that melatonin may be locally synthesized in the olfactory bulb that affects olfactory bulb function [3]. Montufar and et al. suggested in their studies that the main olfactory bulb represents a functional circadian pacemaker in many mammalians during pre- visual stages of development. The olfactory system plays a crucial role in their survival [4]. Nolasco has demonstrated that an olfactory bulb contains an independent circadian pacemaker as lesions of the suprachiasmatic nucleus abolish circadian rhythm in locomotor behaviour but not those of period1 (per1) gene expression in the olfactory bulb. In addition, there is a circadian rhythm sensitive to the olfactory discrimination in the olfactory bulb of the rat and rabbit [5].

The ablation of olfactory bulbs in the rat induces prominent behavioral changes that are not limited to the sensory deficit [6]. The mammalian olfactory system regulates various integrative and multiple functions including social behaviors, reproductive functions, emotional responses, and physiological regulation [7]. Olfactory bulbs have an impact on the effects of photic information on the circadian timing system [8]. Granados showed that the olfactory bulb has a master circadian pacemaker that each night increases olfactory responsivity, drives rhythms, and interacts with the suprachiasmatic nucleus to coordinate other daily behaviors [9]. The effects of the olfactory stimuli on haemostasis in the human support the viewpoint that physicochemical processes and simultaneous information act together in parallel to play a vital role in the life activities of the human organism [10]. Recently, a report showed that the chronobiological patterns

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should consider analyzing activity levels of coagulation factors [11]. The olfactory stimuli through autonomic mechanisms affect the time of blood coagulation as an integral sign of human homeostasis [10]. Thrombin is a major driving force in the growth of thrombus and the primary activator of platelets at the site of thrombus formation [12]. In addition, the hemostatic system is involved not only in the maintenance of the liquid state of the blood, vascular wall resistance, and the arrest of bleeding from injured vessels but also in the regulation of vascular permeability and hemodynamics [13]. Physical activity modifies blood hemostasis and activates fibrinolysis and blood coagulation [14]. Various investigations have proven that strenuous exercise shortens the time of activated partial thromboplastin and leads to an increase in thrombin generation markers [14, 15].

Physical activity has a significant effect on the coagulation system based on its intensity, duration, and type [16]. Exhaustive exercise changes fibrinolysis and blood coagulation [17] and it has been shown that exercise significantly shortens activated partial thromboplastin time and increases factor VIII activity [18]. In addition, blood haemostasis is a complex interaction among platelets, coagulation, and fibrinolysis. According to the previous studies, the intensity of acute exercise is a critical factor affecting blood platelet function [19]. Various investigations showed an increased platelet count of 18-80% immediately after treadmill or bicycle exercising [20]. Waha and coworkers demonstrated the increased t-PA levels in response to resistance exercise [21]. As an interesting probability, thrombin plays a role in the activation of platelet induced by strenuous exercise. Also, exercise increases fibrinolysis and blood coagulation as evidenced by increased tissue plasminogen activation and prothrombin fragment in the plasma [22]. The increase in fibrinolytic and clotting activity induced by exercise has been extensively proven in humans, both for near-maximal and maximal effects; the increased fibrinolytic activity appears in the counterbalance of the exercise-induced increase in coagulability [23]. Few investigations exist on the relationship between the exercise, olfactory bulb, and changes in the coagulation and thrombin time. Thus, the objective of this investigation was to evaluate the effect of the olfactory bulb and physical activity on changes in the coagulation factors in rats.

Materials and Methods

Animal care and selection

30-days old Male Wistar rats (n=60), weighing about 90-100 gr were used in these experiments. The animals were housed at an ambient temperature of 25 ± 2ºC under a 12h/12h light-dark cycle and acclimated to these conditions for 10 days before using in the experiments. All rats had free access to water and the standard feed. Animals were used under the ethical approval of the department.

Experimental design and animal grouping

Animals were divided into 2 groups, 30 rats in each group of the control group (without olfactory bulbectomized) and experimental group (olfactory bulbectomized). In each group, rats were divided into 3 subgroups: short-time (n=10) (5 minutes of physical activity), long-time (n=10) (with 20 minutes of physical activity), and control group (n=10) (without physical activity). To determine the coagulation time, blood samples were collected from the rat tail tip in different stages as before olfactory bulbectomy, after olfactory bulbectomy, and on the olfactory bulbectomy after a short-time and long-time physical activity from the experimental group [24].

Surgical procedure and olfactory bulbectomy

Animals were deeply anesthetized during all surgical procedures, with ketamine 50 mg/kg BW and xylazine 10 mg/kg BW by intraperitoneal injection and submitted to the surgery room according to Leonard and Tuite in 1981 [25]. In brief, the anesthetized rats were put in a stereotaxic apparatus for small animals and skull covering the bulbs was exposed by skin incision and a burr hole was drilled, through which both olfactory bulbs were removed by suction with a hypodermic needle attached to a water pump. Finally, the burr hole was filled with bone wax to avoid further bleeding; after the application of antibiotic powder (Neomycin), the skin was closed with Histoacryl and the rats were returned to their home cages [25]. Ten days after olfactory bulbectomy in experimental and control groups, thrombin time was determined.

Physical activity procedure and swimming test

Rats were put in the center of a plastic pool (55 * 35* 30 cm) with vertical walls, filled with 20 cm of water at 25°C. This large pool dimension is more suitable for mice testing [26]. Then, the rats were observed for 5 minutes and 20 minutes.

Determination of thrombin time in tissues

Rats were killed and then, the autopsy was done on all rats. Blood, liver, heart muscle, spleen, lung, brain, kidney, skeletal muscle, and intestine tissues were isolated. After isolation of the mentioned tissues, they were weighted on the calibrated and accurate scale and 500 mg of each tissue was detached and crushed on the special mortar. Detached tissues were mixed with 5 ml physiological serum solution (NaCl). After completing the crushing of each tissue, samples of the prepared solution tissues and blood were poured on the sodium oxalate test tube. Then, test tubes were centrifuged at 1500 rpm. Thrombin time was measured for each tissue after preparing and documenting the plasma from the mentioned tissues [27].

Statistical analysis

All results were expressed as mean ± SD with the range in parentheses. Principles of Q.F. Lakin's were used to analyze the groups' data. Statistical significance was obtained at $p < 0.05$.

Results

The changes in the thrombin time responses to physical activity (short-time, 5 minutes) are presented in Table 1. Our results showed that thrombin time (TT) on different tissues significantly decreased in the physical activity (PHA) group compared to the group without physical activity (NPHA) ($P < 0.001$). Our data clearly demonstrated that the greatest decrease in TT was observed in the liver tissue. Also, the data presented that long-time (20 min) PHA significantly decreased TT in different tissues in the PHA group compared to the NPHA group ($p<0.001$) and a greater decrease was observed in the liver tissue (Table 2). In addition, as shown in Table 3, TT on different tissues significantly decreased with the exception of blood tissue in the olfactory bulbectomy (OB) rats with short-time physical activity as compared to the rats without olfactory bulbectomy (NOB) ($p < 0.001$). Also, our results showed that long-time PHA significantly increased TT in different tissues in OB rats as compared to NOB rats ($p <0.001$), and a greater increase was observed in the liver tissue (Table 4). According to the data presented in Table 5, the coagulation time (CT) significantly decreased in OB rats after short-time physical activity as compared to the control group (NOB with short-time physical activity) ($p<0.001$). In contrast, after a long-time physical activity, CT significantly increased in OB rats as compared to the control group (NOB with long-time physical activity) ($p <0.001$).

Discussion

The results obtained in the present investigation suggest that physical activity significantly decreased TT and long-time physical activity had a more decreasing impact on TT than short-time physical activity (Tables 1 and 2). Physical activities are known to have an important effect on blood hemostasis [18, 28]. Peat et al. suggested that the activated partial thromboplastin time decreased immediately after the exercise in both inactive and active people [29]. In another study, the effect of one aerobic training session in middle-aged and young men was studied and no change in prothrombin time and a significant decrease in aPTT was reported [30]. The effect of muscular exercise on the blood coagulation has been indicated in the subject of several investigations in both humans and animals [31]. Physical activity modifies the blood hemostasis and significantly shortens activated partial thromboplastin time and increases factor VIII activity [18]. Swimming seems to cause the clotting system activation by increasing fibrinolytic activity [32]. It is well understood that physical activity induces various effects on blood hemostasis by reducing the inflammation and coagulation, which leads to the reduction of mortality. Also, a recent study showed that aerobic exercise accelerates blood coagulation and activates blood fibrinolytic activity [33]. In this regard, it is known that as the stimulus responsible for exercise-induced increase in plasma, von Willebrand factor and coagulation factor VIII content seems to be mediated by b-adrenergic receptors through a nitric oxide-dependent mechanism, the haemostastic system could be conditioned by endothelial function and be modified throughout the aging processes [34]. Also, based on a marathon study, after exercise, despite an increased level of *B*-thromboglobulin, platelet aggregation decreased [35]. Platelet activation during exercise may be related to shear stress causing endothelial damage, increase in plasma thrombin generation, catecholamines, and mobilization of more active platelets from the reticuloendothelial system [36]. Based on the results presented in this study, it was observed that TT significantly decreased in different tissues in OB rats after short and increased after the long-time physical activity. (Tables 3 & 4). Abdi and coworkers demonstrated in their studies that glucose levels, PTT, T, and TT decreased after olfactory bulb in rabbits [37]. Also, our data showed that CT significantly decreased in OB rats after physical activity (short-time), but CT significantly increased after long-time physical activity in OB rats (Table 5). Kim showed that moderate exercise in the heat significantly increased platelet aggregation, which is indicated by reduced CT, while it was not changed in non-hyperthermia exercise conditions [38]. Also, Amawi showed that animals went through 5- minute physical activity and there was no statistically significant variation in the blood CT of samples. However, there was a shortening in the blood CT for a prolonged physical activity [14]. It has been demonstrated that exogenously administered melatonin decreases the skin oxidant damage and normalize activated blood coagulation induced by thermal trauma [39]. A dose-dependent relationship has been reported between the coagulation activity and plasma concentration of melatonin [40, 41]. Therefore, the result of the present study shows the role of the olfactory bulb on changes in thrombin time and coagulation time. Interestingly, our data showed that long-time physical activity caused CT increased in OB rats, but a short-time physical activity decreased it. One of the possible explanations for this is that physical activity effects may be more effective than circadian rhythms' effect on the coagulation time change. Researchers have shown that exhaustive exercise alters fibrinolysis and blood coagulation [42]. In this regard, investigators have found that an increase in the components of the factor VIII complex and a shortening of whole blood clot lysis time occur after exercise [43]. After a strenuous, short-term exercise in male individuals with varying fitness showed signs of increased fibrinolysis and blood coagulation by measuring global tests, factor VII, tPA, and fibrin split products, such as D-dimer and fibrin monomers [44]. Posthuma et al. showed shortened clotting time and increased maximum clot formation after long-term submaximal exercise [45].

Conclusion

The results of the present study indicate that physical activity could decrease thrombin time. Also, TT increased in OB rats. Interestingly, our data showed that after long-time physical activity, CT increased in OB rats but after a short-time decreased. These data clearly indicate that the olfactory bulb on the regulation of circadian rhythms similar to physical activity plays a crucial role in the hemostasis. However, further investigations are necessary to determine the possible mechanisms of physical activity and olfactory bulb in the changes of coagulation and the thrombin system.

Abbreviations:

CT: coagulation time, **TT**: thrombin time, **OB**: olfactory bulbectomy, **NOB**: without olfactory bulbectomy, **PHA**: physical activity, **NPHA**: without physical activity.

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Table 1. Effects of physical activity (short-time) on thrombin time in different tissues of the control group (NOB) in male rats.

Group / Tissue	Non-physical activity		Physical activity		P
	Mean	SD	Mean	SD	
Blood	29.5	1.23	21.3	0.59	<0.001
Liver	41.02	1.60	16.2	0.52	<0.001
Heart muscle	20.01	0.23	17.01	0.73	<0.01
Spleen	21.1	0.90	19.5	0.41	<0.05
Lung	20.0	0.00	17.1	0.50	<0.01
Brain	46.5	1.50	27.2	0.70	<0.001
kidney	34.9	0.50	9.0	0.00	<0.001
Skeletal muscle	39.7	0.40	4.4	0.20	<0.001
Intestine	25.8	0.50	8.5	0.20	<0.001

Table 2. Effects of physical activity (long-time) on thrombin time of different tissues in the control group (NOB) in male rats.

Tissue / Group	Non-physical activity		Physical activity		P
	Mean	SD	Mean	SD	
Blood	29.5	1.23	17.6	0.77	<0.001
Liver	41.01	1.60	7.04	0.64	<0.0001
Heart muscle	20.02	0.53	12.02	0.85	<0.001
Spleen	21.1	0.90	6.01	0.38	<0.001
Lung	20.0	0.00	7.0	0.00	<0.001
Brain	46.5	1.50	9.8	0.30	<0.001
Kidney	34.9	0.50	7.4	0.50	<0.001
Skeletal muscle	39.7	0.40	7.9	0.40	<0.001
Intestine	25.8	0.50	12.6	0.40	<0.01

Table 3. Effects of physical activity (short-time) on thrombin time of different tissues in NOB and OB groups in male rats.

Tissue / Group	Without olfactory bulbectomy		Olfactory bulbectomy		P
	Mean	SD	Mean	SD	
Blood	21.3	0.59	30.01	0.53	<0.001
Liver	16.2	0.52	10.03	0.46	<0.01
Heart muscle	17.02	0.48	10.02	0.39	<0.05
Spleen	19.5	0.41	10.01	0.28	<0.001
Lung	17.1	0.50	31.9	0.70	<0.01
Brain	27.2	0.70	20.1	0.40	<0.05
Kidney	9.0	0.00	30.1	0.50	<0.001
Skeletal muscle	4.4	0.20	40.6	0.50	<0.001
Intestine	8.0	0.20	40.1	0.50	<0.001

Table 4. Effects of physical activity (long-time) on thrombin time of different tissues in NOB and OB groups in male rats.

Group / Tissue	Without olfactory bulbectomy		Olfactory bulbectomy		P
	Mean	SD	Mean	SD	
Blood	17.6	0.77	24.2	0.68	<0.001
Liver	7.02	0.28	33.2	0.53	<0.001
Heart muscle	12.03	0.36	39.9	0.38	<0.001
Spleen	6.04	0.38	20.7	0.41	<0.001
Lung	7.0	0.00	19.4	0.50	<0.01
Brain	9.8	0.30	29.7	0.70	<0.001
Kidney	7.4	0.50	25.1	0.60	<0.01
Skeletal muscle	7.9	0.40	30.0	0.50	<0.001
Intestine	12.6	0.40	16.7	0.50	<0.05

Table 5. Effects of physical activity (short and long time) on coagulation time in OB and NOB rats.

Group / Physical activity	Without olfactory bulbectomy		Olfactory bulbectomy		P
	Mean	SD	Mean	SD	
Short-time	296.9	8.57	219.7	0.93	<0.001
Long-time	100.07	0.39	245.2	0.82	<0.001