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**Research Article**

# SLEEP DEPRIVATION DECREASES LIPOPROTEIN LIPASE AND HEPATIC LIPASE ACTIVITIES IN RAT PLASMA AND ADRENAL GLANDS

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**A B S T R A C T**

Stress has been related to unfavourable concentrations of lipoproteins that may predispose to cardiovascular disease. In this study, we investigated the possible changes in lipases and lipids in the plasma and tissues of sleep-deprived male rats.
Nine rats were distributed into three groups: control (C), sleep deprived (SD) and sleep deprived/rebound (SDR). The three control rats were sacrificed at the beginning of the dark cycle (20:00 h). The remaining rats were deprived of sleep by gentle handling for 24 h, starting at the beginning of the dark cycle (20.00 h). At the end of this period (20:00 h), three rats were sacrificed (SD) and three rats were allowed to sleep for 8 h (SDR) before being sacrificed (04.00 h). SDR animals slept during the dark cycle and therefore, some interference from the circadian cycle cannot be ruled out.
Stress produced by SD in rats caused a decrease in lipoprotein lipase and hepatic lipase activities in plasma (1.9 and 1.4 times in LPL and HL, respectively, vs C) and the adrenal glands (1.6 and 1.7 times in LPL and HL, respectively, vs C). The rats that rebound after SD did not recover the levels of activity of these lipases, which continued to decline after 8 h.
The lipoprotein profile varied in the SD rats but more significantly in the SDR rats. Very low-density lipoprotein in SD rats significantly increased compared with the Control rats, whereas both very low-density lipoprotein, low-density lipoprotein and high-density lipoprotein significantly decreased in SDR rats with respect to both Controls and Sleep Deprivation rats. Phospholipids and cholesterol increased in stressed rats, whereas triacylglycerides and free fatty acids decreased significantly. The adrenal weight increased in both Sleep Deprivation and SDR rats.
Thus, the acute stress produced by sleep deprivation leads to alterations in the plasma and tissue lipases and plasma lipids, which do not always recover after the cessation of stress.



## INTRODUCTION

Sleep is considered critical for the maintenance of health [1] and the support of life [2]. Some of the clinical states associated with abnormal sleep include pulmonary and cardiovascular disorders, cerebrovascular disease, thrombotic disease, epilepsy, arthritis, mood disorders, chronic pain, and shortened lifespan [3,4]. Previous metabolomics-based research on human beings and rats confirmed that a series of metabolites could experience changes due to sleep restriction [5,6]. Stress, defined as any external or internal alteration that forces the organism to adapt to compensate and maintain homeostasis, often causes a decrease in the plasma insulin levels and an increase in cathecholamine [7], glucagon and glucocorticoids [8].

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As an enhancer of the central nervous system excitation, the serum corticosterone is an important hormone responsible for stress in rats [9]. Increased serum corticosterone is considered a biological indicator of sleep restriction [10].

The phenomenon of stress, which occurs widely in both nature and the human society, can be defined as a phylogenetically developed response of an organism to agents that pose a threat to its overall well-being [11].

Stress involves the activation of both the sympato-medullo-adrenal axis (which activates catecholamine release) and the hypothalamus-hypophysis-adrenal axis (which leads to glucocorticoid release). Catecholamines and glucocorticoids act on their target tissues, provoking a metabolic response that prepares the organism for the reaction known as “fight or flight”. This metabolic response is characterized by an increase in the available energy substrates. The cardiac rate and blood

pressure also rise [12]. A previous study in our laboratory [13,14] described that in rats fed a standard diet, acute and/or chronic stress produced by body immobilization induced a notable response in lipid metabolism (increase in plasma free fatty acids (FFA) and glycerol), lipoprotein metabolism (decrease in plasma triacylglycerols (TAG) and increase in total cholesterol) [14], and lipoprotein lipase (LPL) activity (decrease in mesenteric and epididymaladipose tissue and increase in muscle, heart and adrenals) [13]. These changes suggest that catecholamines and glucocorticoids, which are secreted and synthesized under such conditions, may alter the LPL activity directly or indirectly in various tissues. It has been reported that both adrenaline and isoproterenol are capable of increasing LPL activity in the plasma, mainly released from adipose tissue [15]. Glucagon and glucocorticoids do not affect the murine neonatal hepatic lipase (HL) [16,17] nor murine adult HL [18]. The adult HL activity [16,18] has been observed to decrease when the plasma catecholamine levels are high. Long-term sleep restriction may affect the blood lipoprotein levels [4].

LPL is the primary enzyme responsible for the hydrolysis of circulating triacylglycerols (TAG) and thus provides fatty acids (FA) to LPL-rich tissues. Both plasma TAG-rich lipoproteins (chylomicrons and VLDL) are LPL substrates. Cells responsible for LPL synthesis are parenchymal cells in the tissue [19].

HL is involved in the metabolism of the remnant lipoproteins [20] and triglyceride rich-high density lipoproteins-2 ($HDL_2$) [21]. Because of the hydrolysis of both TAG and PL, HL promotes the uptake of HDL cholesterol by the liver [22]. Functional HL was observed in the capillaries of both adrenals and ovaries [23], and it was suggested that the enzyme in these tissues might originate in the liver. Moreover, HL in the plasma is detectable in non-heparin plasma [24].

Previously, we demonstrated that sleep deprivation changes the expression of two nucleoside transporters, CNT2 and ENT1 (high-affinity adenosine-preferring concentrative and equilibrate transporter, respectively) in the rat central nervous system [25]. In the present study, we examine the changes in lipases (LPL and HL) and plasma lipid parameters during sleep deprivation and recovery of this stress inrats.

## METHODS

### *Animals*

Adult male Sprague-Dawley (180–200 g) rats were used for sleep deprivation studies[26]. The rats were maintained at the animal facilities of the University of Barcelona until used. All efforts were made to minimize animal suffering and reduce the number of animals used. The experimental procedures were carried out in accordance with the European Communities Council Directive (86/609/EEC).

### *Sleep deprivation*

Basing on sleep deprivation model previously describe [26,27] and used to adenosine transporter studies in our group [25] and others [28], nine rats were distributed into 3 groups: control (**C**), sleep deprived (**SD**) and sleep deprived/rebound (**SDR**). The three control rats were sacrificed at the beginning of the dark cycle (20:00 h). The remaining rats were deprived of sleep by gentle handling for 24 h, starting at the beginning of the dark cycle (20:00 h). At the end of this period (20:00 h), three rats were sacrificed (SD), and three rats were allowed to sleep for 8 h (SDR) before being sacrificed (04:00 h). SDR animals slept during the dark cycle, and therefore, some interference from the circadian cycle cannot be ruled out. The animals were sacrificed with carbon dioxide. Blood samples were collected in tubes containing EDTA. Plasma was obtained by centrifugation (2500 rpm, 15 min, 4 °C). Tissues were collected, weighed, frozen and stored at -80ºC.

### *Protein and glucose determination*

Protein content was determined using a colorimetric assay [29]. Glucose was determined following the instructions of the commercial kit for Glucose (Roche Diagnostics).

### *Lipids determination*

Free and total cholesterol (FC and TC, respectively), triacylglycerides (TAG), phospholipids (PL) and free fatty acids (FFA) were enzymatically analysed by commercial kits and processed in accordance with the manufacturer's recommendations **(**Wako Laboratory Chemicals).

### *Lipoprotein analysis*

Specific agarose gels, commercialized by Biomidi (Kit Midigel Lipo, France), were used for the analysis of lipoproteins and processed in accordance with the manufacturer's recommendations.

### *Preparation of samples for the lipoprotein lipase (LPL) and hepatic lipase (HL) assay*

The two adrenal glands and approximately 100 mg of liver were homogenized on ice with 0.5 ml and 1 ml, respectively, with buffer pH 7.4 [10 mM HEPES, 1 mM EDTA, 1mMDTT, 5 U/mL heparin], in a Polytron homogenizer[30]. An aliquot of these homogenates was used for protein determination with Bradford assay [29] and the rest were centrifuged at 1000 g for 10 min at 4 °C. Clear supernatants were used for LPL and HL assay. LPL activity was assayed in the plasma, liver and adrenal glands, which contain hepatic lipase (HL)**,** in addition to LPL. The results showed that the HL catalytic activity was inhibited before the LPL assay by a 1.30 h-incubation on ice of sample with antibodies to rat HL (1:1). This was necessary because HL cross-reacts slightly in the LPL assay. Antibodies against rat HL consisted of undiluted serum of rabbits immunized against rat HL, purified from the eluates of heparin-perfused rat livers. The 1:1 ratio of sample to rabbit serum used for this step caused 100% inhibition of the HL enzyme in samples with very high active HL content [30]. Each samples was titrated in duplicate, in total 6 values for plasma or tissue.

### *LPL activity assay*

LPL was determined essentially as previously described [17]. The assay mixture contained 0.6 mM glycerol tri[9,10(n)-$^3$H]oleate (12 Ci/mol), 50 mM $MgCl_2$, 0.05% FFA-free BSA, 3% (vol/vol) serum as a source of apo C-II (preheated at 50 C for 60 min to inactivate lipases), 25 mM PIPES, pH 7.5 and 0.02 mL sample in a final volume of 0.2 mL. Incubation was performed for 30 min at 25 C. The reaction was stopped, free FA was extracted and the amount of [$^3$H] oleate was quantified. The production of 1 μmol of oleate per min is 1 U of LPL.

### *HL activity assay*

HL activity was determined according to Ehnholm and Kuusi [31] with minor modifications. The assay mixture used a gum arabic-based emulsion and contained 2.5 mM glycerol tri[9,10(n)-$^3$H]oleate (0.3 Ci/mol), 0.75 M NaCl, 3% FFA-free BSA, 50 mMTris, pH 8.5, and 0.05 mL of sample in a final volume of 0.2 mL. The samples were incubated for 30 min at 25 °C. The reaction was stopped, free FA was extracted, and the amount of [$^3$H]oleate was quantified. The production of1 μmol of oleate per min is 1 U of HL activity. The LPL was inactive in this lipase assay due to high NaCl concentration and the lack of serum cofactor.

### *Statistics*

The results are presented as the mean ± SEM (in some cases when the error is not seen in the graph, this is included in the mean). Differences between mean values from C rats and SD or SDR rats were analysed with the non-parametric method of Kruskal-Wallis test. Individual comparisons were made using Dunn's Multiple Comparison. Statistical comparisons were considered significant when $p<0.05$. Significant differences between the lipoprotein fractions (VLDL, LDL and HDL) of the three animal groups were studied: the control (C), sleep deprived (SD) and sleep deprived/rebound (SDR) groups were assessed by two-way ANOVA (comorbidities and surgery effect, respectively) and the Bonferroni post-test. All statistical analyses were computed using the GraphPad Prism program version 4.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com).

## RESULTS

Plasma glucose has been described as a reliable index of acute stress [32]. Table 1 shows that glycaemia increases significantly ($p<0.01$) in sleep-deprived animals (SD). When the animals were allowed to recover (SDR), the glycemic values tended to normalize. Figure 1A shows the variation in the LPL activity in plasma.

**Table 1** Glucose and lipid concentration in the plasma in the animals of the three groups studied. The glucose and different plasma lipid contents were compared between the SD and SDR groups (º) and with those obtained in the control animals (*) using the non-parametric method of the Kruskal-Wallis test. Individual comparisons were made using the Dunn's Multiple Comparison. Abbreviations used:TAG, triacylglycerides; FFA, free fatty acids; TC, total cholesterol; FC, free, cholesterol; PL, phospholipids. The animal number in each group, n=3. One symbol: $P < 0.05$; two symbols: $P < 0.01$, and three symbols: $P < 0.001$.

| | glucose (mM) | TAG (mM) | FFA (mM) | TC (mM) | FC (mM) | PL (mM) |
|---|---|---|---|---|---|---|
| **C** | 12.70±0,42 | 1,39±0,03 | 0.52±0.04 | 1.10±0.11 | 0.45±0.05 | 1.58±0.07 |
| **SD** | 16.14±0.90 ** | 0,37±0,01 *** | 0.39±0.08 | 1.82±0.02 ** | 0.57±0.0 | 1.69±0.03 |
| **SDR** | 13,13±0,90 º | 1,68±0,05 **.ººº | 0.59±0.05 | 1.49±0.05 **.º | 0.76±0.01 **.ººº | 1.77±0.06 |

Both sleep deprivation (SD) and sleep deprivation with subsequent rebound (SDR) caused a significant decrease ($p<0.001$) in the plasma LPL activity. Conversely, there were significant differences in the plasma LPL activity between SD and SDR ($p<0.01$). The HL plasma activity also significantly decreased in rats stressed with (SDR) or without recovery (SD) ($p<0.001$ and $p<0.01$, respectively) compared with control rats (Figure 1B). No significant differences were observed between these two groups. The specific activity of LPL decreased significantly compared with the C group (0.013 ± 0.0 mU / mg protein) in the SD rats (0.007 ± 0.001 mU / mg protein; SD versus C, $p<0.001$) and in SDR (0.004 ± 0.001 mU / mg protein; SDR vs. C, $p<0.001$ and SDR vs SD, $p<0.05$).

**Figure 1** Burgaya *et al*

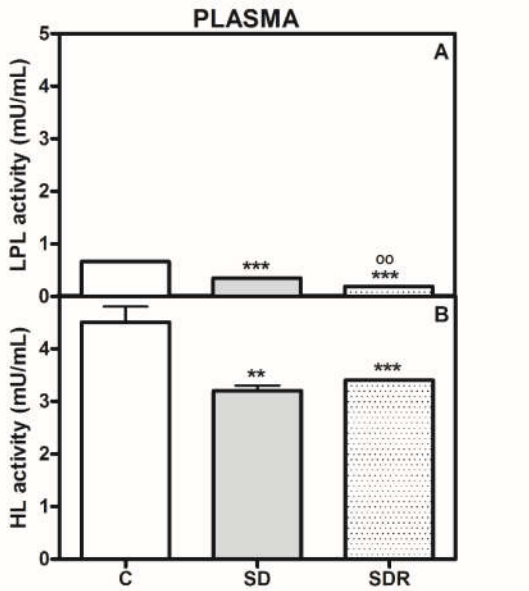


**Figure 1** LPL and HL activities analysed in the plasma of the three groups studied: sleep deprived (SD), sleep deprived/rebound (SDR) and control (C) animals. The LPL (panel A) and LH (panel B) activities in plasma were compared between the SD and SDR groups (º) and with the control animals (*) using the non-parametric method of the Kruskal-Wallis test. Individual comparisons were made using Dunn's Multiple Comparison. We have conserved the same scale for the two enzymes (A and B) to better appreciate the differences between them.The animal number in each group, n=3 in duplicate. In some cases when the error is not seen in the graph, this is included in the mean. One symbol: *, º $P < 0.05$; two symbols: *, º $P < 0.01$, and *, º three symbols: $P < 0.001$.

In Figure 2A, small variations of liver LPL activity were observed between the three experimental groups: C, SD and SDR, but these differences were not significant in any case. The specific activity of LPL increased in SD rats (0.24 ± 0.01 mU / mg protein) compared with the controls (0.16 ± 0.0 mU / mg protein, SD versus C, $p<0.05$).

**Figure 2** Burgaya et al

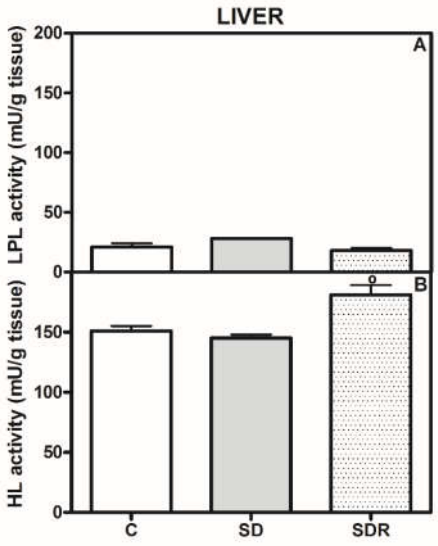


**Figure 2** LPL and HL activities analysed in the liver of the three groups studied: sleep-deprived (SD), sleep deprived/rebound (SDR) and control (C) animals. The LPL (panel A) and LH (panel B) activities in the liver in the SD and SDR groups were compared (º) with each other and with those obtained in control animals (*) using the non-parametric method of the Kruskal-Wallis test. Individual comparisons were made using Dunn's Multiple Comparison. We have conserved the same scale for the two enzymes (A and B) to better appreciate the differences between them.The animal number in each group, n=3 in duplicate. In some cases when the error is not seen in the graph, this is included in the mean. One symbol: *, º $P < 0.05$; two symbols: *, º $P < 0.01$, and three symbols: *, º $P < 0.001$.

**Table 2** The weight of the tissues and the amount of protein per gram of tissue in the animals of the three groups studied. The weight tissues and protein content were compared between the SD and SDR groups (º) and with those obtained in the control animals (*) using the non-parametric method of the Kruskal-Wallis test. Individual comparisons were made using Dunn's Multiple Comparison. The animal number in each group, n=3. One symbol: $P < 0.05$; two symbols: $P < 0.01$, and three symbols: $P < 0.001$.

| | weight (g) | mg prot/g tissue |
|---|---|---|
| adrenals C | 0,023±0,003 | 102.3±9.0 |
| adrenals SD | 0,028±0,0 *** | 93.0±3.3 |
| adrenals SDR | 0,037±0,0 ***,ººº | 77.0±8.2 |
| liver C | 8,4±0,2 | 131,8±2,2 |
| liver SD | 7,5±0,1 * | 147,2±11,8 |
| liver SDR | 8,5±0,0 ººº | 145,7±7,7 |
| plasma C | - | 48,6±0,8 |
| plasma SD | - | 53.0±0,0 * |
| plasma SDR | - | 52.1±0,0 ººº |

However, in the case of SDR, it decreased significantly with respect to controls and SD (0.011 ± 0.0 mU / mg protein; SDR vs C, p<0.001 and SDR vs SD, p<0.01). HL liver activity also varied in the SD and SDR groups with respect to the activity detected in the control rats (Figure 2B), although it significantly increased (p<0.05) in the SDR rats with respect to the activity detected in SD. The liver weight (Table 2) decreased significantly (p<0.05) in SD (7.5 ± 0.1 g) with respect to the controls (8.4 ± 0.2 g). The SDR liver weight (8.5 ± 0.0 g) was recovered to C values and was significantly (p<0.001) higher than that in SD rats.

Adrenal LPL activity (Figure 3A) decreased significantly in both sleep deprived (SD, p<0.01) and sleep deprivation with subsequent recovery (SDR, p<0.01) animals compared with control. A significant decrease (p<0.05) in LPL activity relative to stressed sleep rats (SD) was also observed in SDR rats.

**Figure 3** Burgaya et al

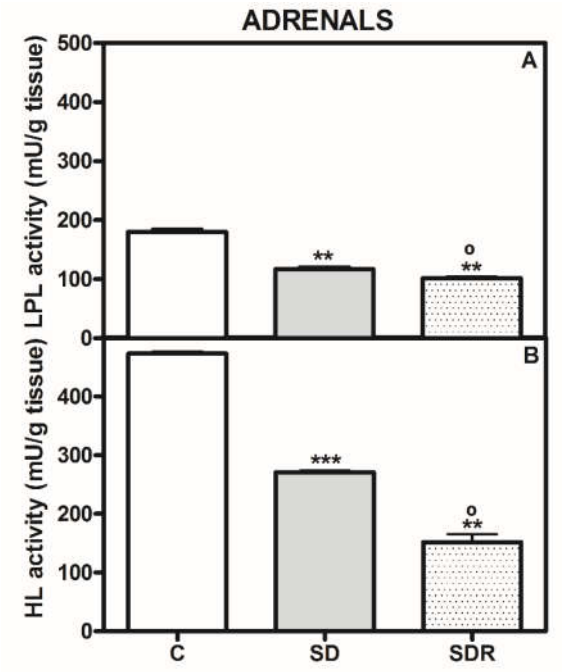


**Figure 3** LPL and HL activities analysed in adrenal glands of the three groups studied: sleep deprived (SD), sleep deprived/rebound (SDR) and control (C) animals. The LPL (panel A) and LH (panel B) activities in the adrenal glands were compared between the SD and SDR groups (º), and with those obtained in control animals (*) with the non-parametric method of Kruskal-Wallis test. Individual comparisons were made using Dunn's Multiple Comparison. We have conserved the same scale for the two enzymes (A and B) to better appreciate the differences between them. The animal number in each group, n=3 in duplicate. One symbol: *,º $P < 0.05$; two symbols: *,º $P < 0.01$, and three symbols: *,º $P < 0.001$.

The pattern of changes observed in HL in the adrenals (Figure 3B) was similar to that observed for the LPL activity in this tissue, although with values more than twice that for LPL and more pronounced differences. Conversely, the weight of the adrenal glands (Table 2) increased significantly in both SD (0.028 ± 0.0 g, p<0.001) and SDR (0.037 ± 0.05 g, p<0.001) compared with control rats(0.023 ± 0.003 g). Moreover, in SDR rats, the weight continued to increase until it was significantly different (p<0.001) with respect to SD.

A significant decrease in the lipoprotein fractions (VLDL, LDL and HDL) was observed only in the SDR group with respect to both control and SD rats, and in this group, only the VLDL fraction was significant compared with the control (Figure 4).

**Figure 4** Burgaya et al

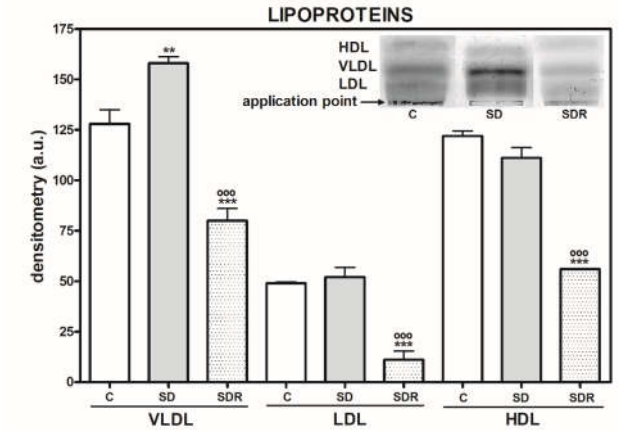


**Figure 4** Evaluation of the different lipoprotein fractions in the plasma of the three groups studied. Significant differences between the lipoprotein fractions (VLDL, LDL and HDL) of the three animal groups studied were assessed by a two-way ANOVA (fraction and stressed, respectively) and the Bonferroni post-test. The SD and SDR groups were compared with each other (º) and with the control animals (*). The animal number in each group, n=3in duplicate. One symbol: *,º $P < 0.05$; two symbols: *,º $P < 0.01$, and three symbols: *,º $P < 0.001$.

For plasma lipids (Table 1), there was a dramatic reduction of TAG in the plasma of SD compared with controls (p<0.001), whereas SDR not only tended to recover the TAG levels of the controls (p<0.01) but also increased above these (see Table 1). The changes observed in both total and free cholesterol (Table 1), followed the same pattern as observed for the TAG, even with similar significant differences. We did not observe significant changes in the PL or FFA (Table 1), the latter tended to decrease in the stressed rats, SD, as observed for the TAG.

Finally, the adrenal and liver weights were found to be correlated with the HL activity in these tissues in SD rats (p<0.05, in both cases) but not in the other two experimental groups.

## DISCUSSION

In previous studies, we have demonstrated that sleep deprivation changes the expression of the two transporters CNT2 and ENT1 (high-affinity adenosine-preferring concentrative and equilibrate transporter, respectively) in the rat central nervous system [25]. In the present study, although preliminary, we examine the changes in lipases (LPL and HL) and plasma lipid parameters during sleep deprivation and recovery of this stress in rat.

Sleep deprivation in the studied animals is considered as acute stress since an increase in blood glucose and adrenal weight, typical markers of acute stress, was observed as described previously [32]. However, once the stress is over, we expected full recovery of the normal levels of individual markers. Although glycaemia tends to recover, it is still high in animals that are allowed to sleep after stress (SDR), while the weight of their adrenal glands increases above the levels of the sleep deprived (SD) rats. Moreover, in most evaluated parameters, we observed that these animals react with values higher than the control animals or significantly lower than the stressed animals. The recovery/rebound time (24 h) is probably not enough to regain normal levels of these parameters, or perhaps some stress was retained as alertness in case the stressing episode was repeated. Because the SDR animals sleep during the dark phase, basing on sleep deprivation model previously describe [26,27], we can not rule out any kind of interference in the circadian cycle.

The LPL activity of a tissue was regulated, among other mechanisms, by the release of the LPL enzyme from the endothelium resulting in an increase in plasma LPL [19,33]. Thus, it has been suggested that the non-esterified fatty acids (NEFA) could increase the release of the active LPL from tissues [34]. In several physiological situations such as fasting [35] and certain types of exercises [36], an increase in LPL activity levels in the plasma have been described. In our study, a significant decrease in the plasma LPL activity in the stressed animals was observed. Moreover, a decrease in the FFA in plasma was observed without ruling out that these FFAs may be diverted to other tissues, such as the muscle. The FFAs in this tissue, in a situation of stress, would be more necessary than in the liver, where they would be re-esterified and exported in the form of VLDL. Recently, Zhan *et al*. [9] observed that rats subjected to chronic sleep deprivation suffered a reduction in all lipid parameters (lipoproteins, TAG, FFA, TC, etc.). Other authors [37] had observed that cholesterol fractions significant increases in LDL and HDL in aged paradoxical sleep deprivation (PSD) rats compared to respective controls, whereas VLDL was significant decreased after PSD in both young and aged animals. However, in humans subjected to sleep restriction, the FFAs increase, which could partially contribute to insulin resistance and increase the risk of diabetes associated with sleep loss [38]. In humans, the increase in PL and TAG suggests that sleep loss might modulate lipid metabolism, which has potential implications for metabolic health in individuals who do not receive adequate sleep [39].

Catecholamines, which increase LPL activity in the muscle and decreaseLPL activity in the WAT [15,36], are the most powerful modulators of tissue LPL. The LPL activity increases in plasma [40] after surgical stress, and stress is a physiological situation where in the catecholamine levels are significantly increased [11].

However, the LPL activity decreased significantly in the plasma. Moreover, the total enzyme activity (not per gram of the tissue) increased in the adrenals, since the weight of these glands increases as in the liver. This same effect had already been observed in mice subjected to chronic social stress [41]. Hepatic lipase (HL) was strongly affected in the adrenal glands, decreasing nearly two-fold, which could be related to the observed total cholesterol increase. Although we did not measure the plasma corticosterone in our animals, other studies [42] did not observe changes in this hormone until after 192 h of sleep loss. Perhaps this is why an increase in HL in the adrenals is not observed. The HL is necessary to capture the circulating cholesterol and promote the synthesis of this hormone, as it occurs in animals subjected to chronic stress [41]. Although in this experiment we did not carry out any control group of the circadian cycle, by previous work in our laboratory [43], we know the behavior of LPL and HL in plasma and tissues.

Recently, we observed a decrease in LPL activity in the liver, adipose tissue (subcutaneous and visceral) and plasma [44] in addition to a reduction in plasma and liver HL, together with a decrease in the different lipids in plasma and tissues, after bariatric surgery in morbidly obese humans [45]. It would be interesting to record the quantity and quality of sleep in obese patients, particularly because many suffer from sleep apnea. Epidemiological and experimental studies have reported that sleep restriction is an independent risk factor for weight gain and obesity. Moreover, sleep restriction is significantly associated with the incidence and prevalence of obesity and several non-transmissible chronic diseases [46].

## CONCLUSION

The animal models allow the use of different tissues, which is limited in the case of humans. Moreover, this study is limited by its small sample size of animals. However, the role of LPL and HL in animals or humans subjected to sleep restriction has been scarcely studied; thus, our study, although preliminary, lays the foundation for the study of these lipases in other tissues and their role in the metabolism of lipids.

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