https://doi.org/10.52973/rcfcv-e34340 Revista Científica, FCV-LUZ / Vol. XXXIV, rcfcv-e34340

An evaluation of Nesfatin–1 levels in Awassi sheep according to the type of birth

Una evaluación de los niveles de Nesfatin–1 en ovejas Awassi según el tipo de parto

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ABSTRACT

The physiological process of birth can cause stress in animals because it affects many mechanisms. The aim of this study was to determine the effect of the type of birth on the Nesfatin–1 level and to explain the relationship with oxidative stress parameters in Awassi breed sheep. The study included a total of 60 sheep with a singleton birth in 3 groups: as Group 1 (n:20) including animals that had a normal birth, Group 2 (n:20) that had a difficult birth (dystocia), and Group 3 (n:20) including sheep that gave birth by caesarean section. Blood samples were taken from the sheep in all the groups within 10 min of the birth, for the measurement of Nesfatin–1, total antioxidant capacity (TAS), and total oxidant capacity (TOS). The data obtained were examined with One-Way Variance Analysis, and relationships between the data with the Pearson test. Statistically significant differences were determined between the groups in respect of Nesfatin–1, TAS, TOS, and oxidative stress index (OSI) levels (P<0.001). The Nesfatin–1, TOS, and OSI levels were determined to be lowest in the normal birth group and highest in the caesarean birth group (P<0.001). The TAS level was highest in the normal birth group and lowest in the caesarean birth group (P<0.001). A significant negative correlation was determined between Nesfatin–1 and TAS (r=-0.932, P<0.001), and a significant positive correlation was determined between Nesfatin–1 and TOS, and between Nesfatin–1 and OSI (r=0.957, P<0.001; r=0.960, P<0.001, respectively). These results demonstrated a significant difference in Nesfatin–1 level according to the type of birth. Therefore, Nesfatin–1 could be a new biomarker in the determination of oxidative stress in sheep according to the type of birth, and it was concluded that one of the interventions that would decrease oxidative stress after dystocia and caesarean births would be to provide an increase in endogenous Nesfatin–1 because of its antioxidative property.

Key words: Nesfatin–1; oxidative stress; dystocia; caesarean section; sheep

RESUMEN

El proceso fisiológico del nacimiento puede provocar estrés en los animales porque afecta a muchos mecanismos. El objetivo de este estudio fue determinar el efecto del modo de nacimiento sobre el nivel de Nesfatin–1 y explicar la relación con los parámetros de estrés oxidativo en ovejas de raza Awassi. El estudio incluyó un total de 60 ovejas con un parto único en 3 grupos: Grupo 1 (n:20) que incluye animales que tuvieron un parto normal, Grupo 2 (n:20) que tuvo un parto difícil (distocia) y Grupo 3. (n:20) incluyendo ovejas que dieron a luz por cesárea. Se tomaron muestras de sangre de las ovejas en todos los grupos dentro de los 10 minutos posteriores al nacimiento, para medir la Nesfatina–1, la capacidad antioxidante total (TAS) y la capacidad oxidante total (TOS). Los datos obtenidos fueron examinados con Análisis de Varianza Unidireccional y las relaciones entre los datos con la prueba de Pearson. Se determinaron diferencias estadísticamente significativas entre los grupos con respecto a los niveles de Nesfatin–1, TAS, TOS y el índice de estrés oxidativo (OSI) (P<0,001). Se determinó que los niveles de Nesfatin–1, TOS y OSI eran más bajos en el grupo de parto normal y más altos en el grupo de parto por cesárea (P<0,001). El nivel de TAS fue más alto en el grupo de parto normal y más bajo en el grupo de parto por cesárea (P<0,001). Se determinó una correlación negativa significativa entre Nesfatin–1 y TAS (r =-0,932, P<0,001), y una correlación positiva significativa entre Nesfatin–1 y TOS, y entre Nesfatin–1 y OSI (r =0,957, P<0,001; r=0,960, P<0,001, respectivamente). Estos resultados demostraron una diferencia significativa en el nivel de Nesfatin–1 según el modo de nacimiento. Por tanto, Nesfatin–1 podría ser un nuevo biomarcador en la determinación del estrés oxidativo en ovejas según el modo de nacimiento, y se concluyó que una de las intervenciones que disminuirían el estrés oxidativo tras distocia y partos por cesárea sería proporcionar un aumento en Nesfatin–1 endógeno debido a su propiedad antioxidante.

Palabras clave: Nesfatin–1; estrés oxidativo; distocia, cesárea; oveja

Received: 19/10/2023 Accepted: 04/03/2024 Published: 12/06/2024

INTRODUCTION

Birth is the process of the removal of the fetus together with fluids and membranes of the offspring from the maternal organism at the end of pregnancy, which is specific to the species [1]. Dystocia is defined as a life-threatening condition for both mother and newborn due to birth not having occurred in a certain time and that cannot occur without some kind of intervention [2]. Dystocia may be of fetal or maternal origin [3, 4]. and causes severe decreases in reproductive performance and puerperal infections. It is also of great importance that there may be complications that can result in the death of the offspring and even the mother [3, 5, 6]. A caesarean section operation is a laparotomy method to remove the fetus by making an incision in the abdominal wall and uterus, which is used when vaginal route delivery is high risk or not possible. This is widely used in all living creatures in cases of dystocia, where the mother, fetus, or both are at risk [6].

Oxidative stress develops when there is an imbalance in cells because of an increase in free radicals or a decrease in antioxidants. There is a series of special mechanisms that keep this stress under control. When these mechanisms remain insufficient, oxidative damage occurs [7]. When the antioxidant systems are inadequate against oxidative stress, the progression of oxidative damage can cause damage to proteins, lipids, carbohydrates, and Deoxyribonucleic acid (DNA) in cells, resulting in cell dysfunction [8, 9]. Organs and tissues with a high metabolism rate and high energy demands, primarily the muscles, heart, liver, brain, and skin, are affected by high levels of oxidative stress [10].

Nesfatin-1, which was discovered in 2006, is a 9.7 kDa peptide formed of 82 amino acids and is effective in the physiological control of feeding behaviour. It plays a role in body weight control by suppressing the peristaltic activity of the digestive system, ultimately reducing food intake [11]. Non-esterified fatty acid/nucleon binder-2 (NUCB2) is the precursor of Nesfatin-1 [12]. Previous studies have shown that Nesfatin-1 has vital power in the suppression of energy intake through signals coming from peripheral tissues in the brain [13] and is protective against serious metabolic disorders [14]. Biochemical, immunohistochemical, physiological, pathological, and pharmacological studies related to Nesfatin-1 have focused more on humans and some animal species to date [15]. Recent studies have shown antioxidant, anti-inflammatory, and anti-apoptotic effects of Nesfatin-1 in different diseases [16, 17].

The aim of this study was to determine the effect of the type of birth on the Nesfatin-1 level in Awassi breed sheep, and to investigate the correlations between Nesfatin-1 and oxidative stress parameters. There is no previous study in the literature that has evaluated Nesfatin-1 in sheep according to the type of birth, and therefore this study can be considered to contribute to the literature.

MATERIALS AND METHODS

Approval for this study was granted by the Animal Experiments Local Ethics Committee of Harran University (HRÜ-HADYEK)(decision no: 2023/005).

Animal selection and experiment protocol

This study was conducted between February and March 2022 at the Obstetrics and Gynaecology Clinic of Harran University Veterinary Faculty Animal Hospital, located in the Eyyubiye district of Şanlıurfa Province, southeast Türkiye, at an altitude of 517 m, 37.11974 latitude and 38.81990 longitude (average temperature (°C): 6.35, average monthly total rainfall (mm): 65.35)[18]. The animal sample comprised 60 Awassi sheep, aged 2-4 years, each weighing mean 55.24 ± 1.22 kg, with a body condition score ranging from 2-3 (1=Extremely weak, 5=Obese)(2.56 ± 0.06), which had previously given birth at least once, and had no genital system conditions.

The 60 sheep were separated into 3 groups as Group 1 (n:20) including animals that had a normal birth, Group 2 (n:20) those that had a difficult birth (dystocia), and Group 3 (n:20) including sheep that gave birth by caesarean section. Dystocia was defined as a difficult delivery which exceeded 90 min in total, or when there was no progression for 30 min after rupture of the fetal membranes [19]. For sheep that could not deliver despite interventions, a caesarean section operation was performed.

Blood sample collection and laboratory analysis

Blood samples were taken from the vena jugularis of the ewes in all the groups within 10 min of the birth of the offspring. The blood samples were centrifuged (NÜVE NF 200, Ankara, Turkey) at 3000 G or 10 min to obtain serum samples, which were then stored at -20°C until the day of analysis. To determine the serum Nesfatin-1 levels of the sheep in all the groups, a commercial kit was used (Sheep Nesfatin E0095Sh, ELISA Kit – NES BT-LAB kit.). The serum TAS and TOS levels were examined using commercial kits (Total Antioxidant Status, NN21117A, Rel Assay Diagnostics, Mega Tıp, Gaziantep, Türkiye, and Total Oxidant Status NN211290, Rel Assay Diagnostics, Mega Tıp, Gaziantep, Türkiye) and were determined spectrophotometrically at 660nm for TAS and at 530 nm for TOS (Molecular Device SpectraMax M5 Plate Reader, Pleasanton, CA, USA) FIGURE 1. The oxidative stress index (OSI) was calculated as the ratio of the TAS and TOS levels [20].

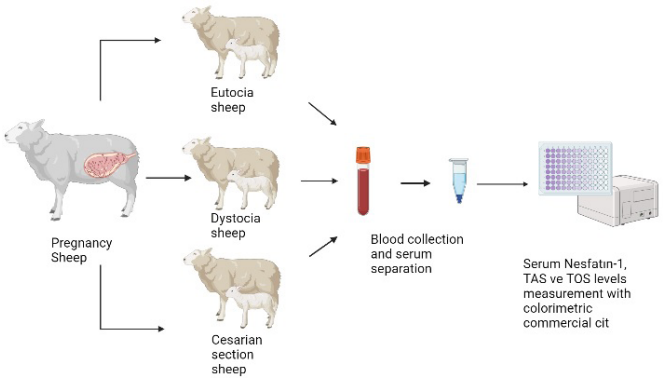

FIGURE 1. Study design for evaluation of Nesfatin-1 levels in Awassi sheep according to the type of birth

Statistical analysis

Data obtained in the study were analyzed statistically using Statistical Package for the Social Sciences (SPSS Statistics for Windows)[21] software. Conformity of variables to normal distribution was assessed using visual (histogram and Q-Q Graphs) and analytical methods (Shapiro-Wilk tests). Descriptive analyses were stated as mean ± standard error (SEM) values for variables showing normal distribution. As the relevant data showed normal distribution, One-

Way Variance Analysis was applied in the comparisons of the groups. Correlations of the data and statistical significance were determined with the Pearson test. The total error margin for statistical significance was determined as 5%.

RESULTS AND DISCUSSION

The Nesfatin-1 levels and oxidative stress parameters according to the type of birth are presented in TABLE I. Statistically significant differences were determined between the groups in respect of Nesfatin-1, TAS, TOS, and OSI levels (P<0.001). The Nesfatin-1, TOS, and OSI levels were determined to be lowest in the normal birth group and highest in the caesarean birth group (P<0.001). The TAS level was highest in the normal birth group and lowest in the caesarean birth group (P<0.001). Significant correlations were determined between the Nesfatin-1 level and oxidative stress parameters (P<0.01). There was seen to be a significant negative correlation between Nesfatin-1 and TAS (r=-0.932, P<0.001), and a significant positive correlation was determined between Nesfatin-1 and TOS, and between Nesfatin-1 and OSI (r=0.957, P<0.001; r=0.960, P<0.001, respectively). There was also determined to be a significant negative correlation between TAS and TOS (r= -0.967, P<0.001) and between TAS and OSI (r=-0.994, P<0.001), and a significant positive correlation between TOS and OSI (r=0.981, P<0.001) TABLE II.

The results of this study present important data that will contribute to the understanding of the effect type of birth on Nesfatin-1 levels and oxidative stress in Awassi breed sheep. The physiological process of birth can cause stress in animals because many mechanisms are affected. It has been stated that a normal birth is a stressful process and abnormal deliveries (dystocia, caesarean) can contribute further to the stress of a normal birth [22].

TABLE I
Oxidative parameters and Nesfatin-1 levels in Awassi sheep according to type of birth

Nesfatin-1 and OSI status	N	Nesfatin-1	TAS	TOS	OSI
		X̄ ± SEM	X̄ ± SEM	X̄ ± SEM	X̄ ± SEM
Eutocia (Group 1)	20	5.10 ± 0.10^{a}	2.00 ± 0.010^{a}	12.81 ± 0.57^{a}	6.36 ± 0.04^{a}
Dystocia (Group 2)	20	7.20 ± 0.08^{b}	1.76 ± 0.009^{b}	16.01 ± 0.86^{b}	9.03 ± 0.06^{b}
Cesarian Section (Group 3)	20	10.06 ± 0.10^{c}	1.57 ± 0.007^{c}	19.01 ± 0.78^{c}	12.07 ± 0.08^{c}
P value (repeated measures ANOVA)		P=0.000 ***	P= 0.000 ***	P=0.000 ***	P= 0.000 ***

^{a,b,c}: Different letters in the same column indicate a statistically significant difference. ***: P<0.001, ANOVA: Analysis of variance, X̄ : mean, SEM: Standard error of the mean. TAS: total antioxidant capacity, TOS: total oxidant capacity, OSI: oxidative stress index

TABLE II
Correlations between Nesfatin-1, TAS, TOS, and OSI in Awassi sheep according to type of birth

Correlation analysis		Nesfatin-1	TAS	TOS	OSI
Nesfatin-1	r	1			
TAS	r	-0.932**	1		
TOS	r	0.957**	-0.967**	1	
OSI	r	0.960**	-0.981**	0.994**	1

**: P<0.01, r: correlation coefficient, TAS: total antioxidant capacity, TOS: total oxidant capacity, OSI: oxidative stress index

Aerobic exercise has a significant effect on energy-regulating hormones such as Nesfatin-1 [23]. Muscle activity induced by aerobic exercise has been shown to lead to significant increases in Nesfatin-1 levels in healthy women [24, 25]. In another study the increase in Nesfatin-1 levels after high-intensity training was shown to be no different from the increase after moderate intensity training [24]. There has been determined to be a significant increase in Nesfatin-1 levels as a response to acute maximal intensity and short-term exercise in normal body weight subjects [26]. The current study is the first to have determined the Nesfatin-1 level in sheep according to the type of birth, and the study results demonstrated significant differences in the Nesfatin-1 level according to the type of birth. In our study, based on the exercise and muscle activity in the above-mentioned literature; muscle activity due to abdominal and uterine contractions that occur during birth may cause an increase in the level of Nesfatin-1 in the circulation. In addition to the change in Nesfatin-1 levels caused by exercise, it may also be because it causes energy regulation in addition to the mechanical effects.

Experimental studies related to Nesfatin-1 have defined anti-inflammatory, anti-apoptotic, and anti-oxidative properties of Nesfatin-1 [27, 28, 29]. Ayada *et al.* [11] concluded that Nesfatin-1 could play a protective role against ischaemia and reperfusion [11]. It has also been reported that by reducing apoptosis, inflammation, and oxidative stress, Nesfatin-1 has a cardioprotective effect in conditions of myocardial damage [16]. Tang *et al.* [30] reported anti-oxidative and anti-apoptotic effects of Nesfatin-1 in rats through neuroprotective effects against subarachnoid bleeding which inhibits apoptosis and causes brain damage. Özsavci *et al.* [31] and Kolgaziet *et al.* [32] stated that the anti-oxidant effects of Nesfatin-1 could improve stomach damage, and Jiang *et al*. [29] showed that the kidneys could be protected against ischaemia reperfusion damage by reducing the oxidative expression of Nesfatin-1. In a rat model study by Tamer *et al.* [33] Nesfatin-1 was shown to have anti-oxidant, anti-inflammatory, and anti-apoptotic effects on testis dysfunction caused by testis torsion. Nesfatin-1 was found to protect spermatogenic cells in the rat testes by reducing proinflammatory cytokine expression, suppressed apoptosis, and degeneration of tubules, and by healing oxidative damage [34].

In our study, the highest level of Nesfatin-1 was determined in the sheep group that had undergone caesarean section operation in which the oxidative stress level was highest, and the lowest was in the normal birth group with the lowest oxidative stress. The reason for this is thought to be that the increase in Nesfatin-1 level is a defence system of the body, and the anti-oxidative property of Nesfatin-1 decreases oxidative stress rapidly and with the least tissue damage. The main shortcoming of our study is that measurements were not taken at certain time intervals after birth to clearly see this effect. The anti-oxidant effect of Nesfatin-1 treatment is shown by the prevention of over-production of intracellular reactive oxygen species (ROS), thereby protecting the balance of the oxidant/antioxidant systems, lowering the levels of lactate dehydrogenase and malondialdehyde, and increasing levels of superoxide dismutase, catalase, and glutathione [29].

Fouad *et al.* [34] measured TAS levels in Egyptian buffalo (*Bubalus bubalis*) according to the type of birth, and higher TAS levels were determined in the animals with a normal birth compared to the group with dystocia. In another study, the serum TAS levels of cows with dystocia were found to be lower, although not at a statistically significant level, than those of cows with a normal birth [35]. Kızıl *et al.* [36] examined the effects on oxidative stress parameters in cows according to the type of birth, and determined differences between the normal, dystocia, and

caesarean birth groups. The highest oxidative stress was determined in the caesarean birth group but the differences were not at a statistically significant level. In a study by Akkuş *et al.* [37] to determine the TAS, TOS, and OSI values in Aleppo goats according to the type of birth, higher TAS levels and lower TOS and OSI values were determined in the normal birth group compared to the dystocia group. In another human clinical study, Noh *et al.* [38] reported that antioxidant capacity was higher in patients who underwent a planned caesarean section delivery compared to those with a normal vaginal route birth, and both mother and newborn were exposed to greater oxidative stress during caesarean delivery. In the current study, differences were seen in the TAS, TOS, and OSI values according to the type of birth, consistent with the findings in literature.

Higher TAS values and lower TOS and OSI values were determined in the normal birth group compared to the dystocia group, and in the dystocia group, higher TAS values and lower TOS and OSI values were determined compared to the caesarean group. The reason for this was thought to be that the contractions occurring in both the skeletal and uterus muscles during labour increase ROS formation. As a result of the increased ROS formation, oxidative damage of lipids, proteins, and DNA has been reported [39]. It has also been shown that oxidative stress is induced by long-term or shorter-term maximal aerobic exercise [40]. There may be significant effects of aerobic exercise on oxidative stress parameters, decreasing antioxidant parameters and increasing oxidant parameters. All these data lead to the hypothesis that oxidative stress may be present during normal and difficult births. Although some studies have shown a great effect of the formation of free radicals in a caesarean delivery, it is thought that the surgical intervention could contribute to lipid peroxidation [41].

CONCLUSIONS

In conclusion, the results of this study demonstrated a significant difference in the level of Nesfatin-1 according to the type of birth. Negative correlations were obtained between Nesfatin-1 and total antioxidant capacity, and positive correlations were obtained between Nesfatin-1 and total oxidant capacity. Therefore, Nesfatin-1 could be a new biomarker in the determination of oxidative stress in sheep according to the type of birth, and it was concluded that one of the interventions that would decrease oxidative stress after dystocia and caesarean births would be to provide an increase in endogenous Nesfatin-1 because of its antioxidative property.

ACKNOWLEDGEMENTS

The authors thank the sheep owners for their kind co-operation throughout the study.

Conflict of interests

The authors have read and approved the article, and have no conflict of interests to declare.

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