Variations in the coding of melatonin receptor gene MTNR1A of Iraqi sheep breed

Rahawy, M. A.[1]; Al-Timimi, I. H.[2] , Najwa, Sh. Ahmad[3] and Ani A.A[4]

[1]Department of Surgery and Obstetrics, College of Veterinary Medicine, Mosul University, [2]College of Veterinary Medicine, Baghdad University, [3]Molecular Department of Biotechnology Research Center, Al-Nahrain University.[4] Iraq Agricultural Researches Ministry of Agriculture.

E-mail: mohammedrahawy@yahoo.com

Received: 19/5/2016

Accepted: 13/7/2016

Summary

The aim of the study was found variation of melatonin receptor gene by sequence analysis, investigation in association between MTNR1A polymorphisms with any variation in allele's frequency of the mutations C606T and G612A of the *MTNR1A* gene in the Iraqi local sheep lambing out of season. Blood samples were randomly collected from 60 ewes from *Agriculture* Research-Ruminant Researches Station Breeding Station, Baghdad. Genomic DNA was isolated using a Geneius TM Micro gDNA Extraction Kit. A large fragment of exon 2 of *MTNR1A* gene was amplified by PCR using specific primer pairs. The PCR product was sequencing 20 samples of *MTNR1A* gene was performed by National Instrumentation Center for Environmental Management (nicem). The result recorded that sequencing of Ovisaries breed local Iraqi ewes lambing in breeding season genotype rr appeared 100%compatibility with standard, Sequence ID: gb|HQ658147.1|, and have number score (1354) bits there was no any polymorphism in melatonin receptor type 1A (MTNR1A) gene, from 76-808 number of nucleotide from gene of Gene Bank. Sequence product from Iraqi ewes lambing out breeding season have genotype RR appeared ٩٢% compatibility with and Sequence ID: gb|HQ658147.1|, and have number score (896) bits There was high polymorphism in melatonin receptor type 1A gene, from 130-710 number of nucleotide from gene of Gene Bank. The genotype RR that were fifteen only which are identical (G120T, G502C, T512G, T525G, T546A,C567T, T579A, T582C, C605G, A611T, A614T, C620T, G624T, C629T and T642A) that change of amino acid specialty C605G that change Proline to Alanine while four silent mutation (G328C, G499C, C604T and C609A) without amino acid change in spring (out-of-season) breeding in Iraqi local sheep.

Keywords: MTNR1A gene, Polymorphism, Iraqi sheep.

Introduction

Selection for fertility in a fall-lambing sheep flock suggest that selection can be used to improve fertility in year around breeding flocks according toAl-Shorepy and Notter (1). Alsoit has been reported that selection on autumn-lambing ability not only can result in ewes with shortened seasonal anoestrus but also lesser selectivity to long day photoperiods (2). This implies that ewes can be genetically improved for out-of-season lambing and thereby accelerated lambing schemes (3). The gene for MT1, melatonin receptor 1A gene (*MTNR1A*), consists of two exons divided by an approximately 8 000 base pair (bp) long intron. Amplifications of most of the exon II have been carried out in PCR reactions with primers that start at position 285-304 and ends at position 1108-1089 of the ovine MTNR1A gene (4). According to (4) lead to the identification of two important SNP ssingle nucleotide polymorphisms, C606T and G612A that marker for breeding out of seasonin the Sarda ewes. This information was matched with the ewes' recorded lambing frequency in the period September-December (out of season) and in the period January-April (normal lambing season). The ewes with genotype C/C had a higher rate of lambing out of season than the ewes with genotype T/T and the heterozygote ewes C/T had similar rates of lambing out of season and normal lambing season. (5) Eight mutations were founded on the MT1 receptor that C558T, G735A, G753A, C843T, and C1053T without amino acid change while C845A lead to Ala. To Asp., A1073G lead His, to Arg. and A1081G lead Ile. to Val. The aim of this study is to investigate the association between MTNR1A polymorphisms with any variation in allele's

frequency of the mutations in the coding sequence of the MTNR1A gene in the Iraqi local sheep lambing out of season.

Materials and Methods

Sixty local Iraqi ewes from the state board for Agriculture Research Ruminant Researches Station- Ministry of Agriculture (Agurgof) Baghdad in latitude 33.325 longitude 44.422 from March 2015 to March 2016 were included. Ewes were divided into 2 main groups depending on the season of lambing as follows: The 1st group include ewes which lambed from February to last April. The 2nd group include ewes which lambed from October to last December. Lambs were weaned before day 73 of age, then ewes again are placed with breeding rams to begin the next season. Ten milliliters of blood were collected from the jugular vein in EDTA coated tubes, for DNA extraction using a commercial (Geneaid Biotech Ltd GMB 100)in laboratory of Molecular Department of Biotechnology Research Center-Al-Nahrian University/Baghdad. A fragment with the size of 824 bp from exon II of MTNR1A gene were amplified with a specific primer: forward: 5'-TGT GTT TGT GGT GAG CCT GG-3', and reverse: 5'-ATG GAG AGG GTT TGC GTT TA-3') pairs. The total volume of PCR reaction was 25 µl. The amplification reactions was started according to (6) with following temperatures profile consisting of an initial denaturation at 94°C for 5 min, followed by at40 cycle program with denaturation at 94 °C for 1 min, annealing at 54.3 °C for 1 min, elongation at 72 °C for 1 min and final elongation at 72 °C for 12 min. PCR band was visualized by electrophoresis and captured by gel documentation system to the observed band.Sequencing of MTNR1A gene was performed by National Instrumentation Center for Environmental Management (nicem) online at (http://nicem.snuac.kr/main/?en_skin=index.html), biotechnology lab, machine is DNA sequencer 3730XL, Applied Biosystem), Homology search was conducted using Basic Local Alignment Search Tool (BLAST) program which is available at the National Center Biotechnology Information (NCBI) online at (http://www.ncbi.nlm.nih.gov) and BioEdit program.

Results and Discussion

The sequencing of ovis melatonin receptor 1A (MTNR1A) gene,amplified product gene have size 824 pb from 20 samples (ten sample from ewes lambing in season and ten sample from ewes lambing out season). The result sequencing appeared 100% compatibility with standard Ovisaries breed local Iraqi ewes lambing in breeding season bymelatonin receptor type 1A (MTNR1A) geneof Gene Bank results as shown in (Fig. 1) (Sequence ID: gb|HQ658147.1|, and have number score (1354) bits there was no any polymorphism in melatonin receptor type 1A (MTNR1A) gene, from 76-808 number of nucleotide from gene of Gene Bank.

Score	Expect	Identities	Gaps	Strand
1354 bits(733)	0.0	733/733(100%)	0/733(0%)	Plus/Plus
Query 421	ACTGAAGCCCCAGGACTTCAGGAATTTTGTCACCATGTTTGTGGTTTTTGTCCTCTTTGC			**480**
Sbjct 496	ACTGAAGCCCCAGGACTTCAGGAATTTTGTCACCATGTTTGTGGTTTTTGTCCTCTTTGC			**555**
Query 481	CATTTGCTGGGCTCCTCTGAACTTCATTGGTCTCGTTGTGGCCTCGGACCCCGCCAGCAT			**540**
Sbjct 556	CATTTGCTGGGCTCCTCTGAACTTCATTGGTCTCGTTGTGGCCTCGGACCCCGCCAGCAT			**615**
Query 541	GGCACCCAGGATCCCCGAGTGGCTGTTTGTGGCTAGTTACTATATGGCATATTTCAACAG			**600**
Sbjct 616	GGCACCCAGGATCCCCGAGTGGCTGTTTGTGGCTAGTTACTATATGGCATATTTCAACAG			**675**

Figure, 1: Sequence ID: gb|HQ658147.1||Ovisaries isolate K45 melatonin receptor type 1A (MTNR1A) gene, MTNR1A-r allele, exon 2 and partial cds

Figure (1) recorded that sequencing of Ovisaries breed Iraqi melatonin receptor type 1A (MTNR1A) gene, partial compatibility with NCBI. The bit score is defined as

statistical measure of the moral similarity and the higher value indicates that the high degree of similarity. Result appeared frequently readings sequence of nucleotides of melatonin receptor type 1A (MTNR1A) gene by using Bio Edit program, which was performed by National Instrumentation Center for Environmental Management (nicem). The results of sequencing, genotype rr, however, the sequencing of ovis melatonin receptor type 1A (MTNR1A) gene, amplified product from Iraqi ewes lambing out breeding season appeared 92% compatibility with standard Ovisaries breed Iraqi ewes melatonin receptor type 1A(MTNR1A) gene of Gene Bank results as shown in (Fig. 2 and Table, 1), (Sequence ID: gb|HQ658147.1|, and have number score (896) bits. There were high polymorphism in melatonin receptor type 1A (MTNR1A) gene, from 130-710 number of nucleotide from gene of Gene Bank. The results of sequencing genotype RR that were identified of twenty mutations. Fifteen only which are identical (G120T, G502C, T512G, T525G, T546A, C567T**,** T579A, T582C, C605G, A611T, A614T, C620T, G624T, C629T and T642A) that change of amino acid change specialty C605G that change Proline to Alanine while four silent mutation (G328C, G499C, C604T and C609A) without amino acid change in spring (out-of-season) breeding in Iraqi local sheep shown (Fig. 2 and Table, 1).

Score 1003 bits(543)	Expect 0.0	Identities 654/709(92%)	Gaps 1/709(0%)	Strand Plus/Plus
Query 1	CTATAGTTAACAATGGGTGGAGCCTGAGCTCCCTGCATTGCCAACTTATTGGCTTCCTGA			**60**
Sbjct 72	CTATAGTTAACAATGGGTGGAGCCTGAGCTCCCTGCATTGCCAACTTAGTGGCTTCCTGA			**131**
Query 61	TGGGCTTGAGCGTCATCGGGTCCGTTTTCAGCATCACGGGAATTGCCATCAACCGCTATT			**120**
Sbjct 132	TGGGCTTGAGCGTCATCGGGTCCGTTTTCAGCATCACGGGAATTGCCATCAACCGCTATT			**191**
Query 121	GCTGCATCTGCCACAGCCTCAGATACGGCAAGCTGTATAGCGGCACGAATTCCCTCTGCT			**180**
Sbjct 192	GCTGCATCTGCCACAGCCTCAGATACGGCAAGCTGTATAGCGGCACGAATTCCCTCTGCT			**251**
Query 181	ACGTGTTCCTGATCTGGACGCTGACGCTCGTGGCGATCGTGCCCAACCTGTGTGTGGGGA			**240**
Sbjct 252	ACGTGTTCCTGATCTGGACGCTGACGCTCGTGGCGATCGTGCCCAACCTGTGTGTGGGGA			**311**
Query 241	CCCTGCAGTATGACCCCAGGATCTATTCCTGTACCTTCACGCAGTCCGTCAGCTCAGCCT			**300**
Sbjct 312	CCCTGCAGTATGACCCGAGGATCTATTCCTGTACCTTCACGCAGTCCGTCAGCTCAGCCT			**371**
Query 301	ACACGATCGCCGTGGTGGTGTTCCATTTCATAGTTCCGATGCTCGTAGTCGTCTTCTGTT			**360**
Sbjct 372	ACACGATCGCCGTGGTGGTGTTCCATTTCATAGTTCCGATGCTCGTAGTCGTCTTCTGTT			**431**
Query 361	ACCTGAGAATCTGGGCCCTGGTTCTTCAGGTCAGATGGAAGGTGAAACCGGACAACAAAC			**420**
Sbjct 432	ACCTGAGAATCTGGGCCCTGGTTCTTCAGGTCAGATGGAAGGTGAAACCGGACAACAAAC			**491**
Query 421	CGAAACTCAACCCCCAGGACGTCAGGAATTTTGGCACCATGTTTGTGGTTTTTGACCTCT			**480**
Sbjct 492	CGAAACTGAAGCCCCAGGACTTCAGGAATTTTGTCACCATGTTTGTGGTTTTTGTCCTCT			**551**
Query 481	TTGCCATTTGCTGGGTTCCTCTGAACTACACTGGTCTCGTTGTGGCCTCGGATGCCGACT			**540**
Sbjct 552	TTGCCATTTGCTGGGCTCCTCTGAACTTCATTGGTCTCGTTGTGGCCTCGGACCCCGCCA			**611**
Query 541	GCTTGGCATCCATGATCTCCGAGTGGCTGTATGTGGCTTGATTCAATTTGGAATTTTTCA			**600**
Sbjct 612	GCATGGCACCCAGGATCCCCGAGTGGCTGTTTGTGGCTAGTTACTATATGGCATATTTCA			**671**
Query 601	TCATCTGCCTCTAAGCGATCATAAATGGACAACTGCACCCACACTTTAAGGCACGTCTCT			**660**
Sbjct 672	ACAGCTGCCTCAATGCGATCATATATGGACTACTGAACCAAAA-TTTCAGGCAGGAATAC			**730**
Query 661	ATCATAATTATAGTCTCTGTGCGTAACGCTTTGATGTTCTTGATGGATA			**709**
Sbjct 731	AGAAAAATTATAGTCTCATTGTGTACCACCAAGATGTTCTTTGTGGATA			**779**

Figure, 2: Sample Ovisaries isolate K45 melatonin receptor type 1A (MTNR1A) gene, MTNR1A-R allele, exon 2 and partial cds.

Table, 1: location, type of polymorphism, mutations and amino acid change in sense of melatonin receptor type 1A MTNR1A gene in Iraqi ewes.

No	location of gene bank	Nucleotide change	Amino acid change	Predicted effect	Type of mutation
1	G120T	AGT > ATT	Serine > Isoleucine	Missense	Transversion
2	G328C	CCG> CCC	Proline> Proline	nonsense	Silent Mutation
3	G499C	CTG> CTC	Leucine > Leucine	nonsense	Silent Mutation
4	G502C	AAG> AAC	Lysine > Asparagine	Missense	Transversion
5	T512G	TTC>GTC	Phenylalanine> Valine	Missense	Transversion
6	T525G	GTC >GGC	Valine >Glycine	Missense	Transversion
7	T546A	GTC >GAC	Valine> Aspartic acid	Missense	Transversion
8	C567T	GCT >GTT	Alanine> Valine	Missense	Transition
9	T579A	TTC >TAC	Phenylalanine >Tyrosine	Missense	Transversion
10	T582C	ATT> ACT	Isoleucine >Threonine	Missense	Transition
11	C604T	GAC> GAT	Aspartic acid >Aspartic acid	nonsense	Silent Mutation
12	C605G	CCC >GCC	Proline> Alanine	Missense	Transversion
13	C609A	GCC >GAC	Aspartic acid >Aspartic acid	nonsense	Silent Mutation
14	A611T	AGC> TGC	Serine> Cysteine	Missense	Transversion
15	A614T	ATG >TTG	Methionine> Leucine	Missense	Transversion
16	C620T	CCC> TCC	Proline> Serine	Missense	Transition
17	G624T	AGG> ATG	Arginine> Methionine	Missense	Transversion
18	C629T	CCC> TCC	Proline> Serine	Missense	Transition
19	T642A	TTT> TAT	Phenylalanine> Tyrosine	Missense	Transversion

Two mutations at positions 606 and 612 had been shown by (7). Two mutations at positions 606 and 891 had been evidenced by (5). Another study (8) It has reported the eight mutations (G453T, C606T, G612A, G706A, G783A, G801A, C891Tand C893A) were observed within the limits reported here (positions 305-1088 excluding the primers). Who also find two mutations (C426T, G555A). Five of the mutations were the same reported by (6) for Small Tail Han and Hu sheep breeds. The two mutations in position G706A and C893A led to an amino acid change in site 220 and 282 but they are not fragment of the transmembrane domain of the MT1 melatonin receptor and, in accordance with (9), they should not change the receptor's functionality. Also (4) it has reported that Mutations C606T and G612A have been detected and genotyped using RFLP.

The mechanistic/causal relation between MTNR1A gene polymorphism and seasonality of reproduction is however to be established (10). They reported polymorphism in the promoter site of the gene and found a number of SNPs affecting the binding element for some transcription factors in the promoter site. G706A, a mutation leads to substitution of valine by isoleucine in the fifth transmembrane helix of the receptor, has been exposed to be in close contact with Histidine 211, the mutation of which modified the affinity of receptor to 125I melatonin (11). But, in a study of (12) it has been observed that the sequencing of the Chokla sheep breed Exon II region led to identification of ten mutations. Eight of which were identical (G453T, C606T, G612A, G706A, G783A, G801A, G891A and G893A). Two other mutations (G675A and G931C) were reported in study of (14). It has been did not detect mutations C426T and G555A in Chokla sheep breed as founded by (6) in Merino d'Arles ewes. It has been detected that the mutations G706A, C893A and G931C led to an amino acid change at site 220, 282 and 295, respectively.

The mutation at site G893A led to substitution of amino acid alanine by aspartic acid in the third extracellular loop. Another important mutation G931C, which is being observed first time, seems to be one of the main conformational destabilizing mutations (CDM). Polyphen-2 analysis revealed that this mutation was actually damaging with a score of 0.912. It led to substitution of alanine by proline in the seventh helical transmembrane domain. Helical domains, fixed in hydrophobic lipid environment, are invented of a stretch of 20–30 hydrophobic amino acids. Loop regions between these helical domains are typically hydrophilic. Substitution of alanine by proline may be destabilizing to the stable conformation of the Melatonin receptor1A gene for the following reasons: First, in proline the nitrogen ring is part of a rigid ring and rotation about N\Cα bond is

impossible, acting as a kink in the helical structure. Second, proline has low hydrophobicity index (13) (index) of (−1.6) in comparison to alanine (+1.8).This may impede the interaction with lipid moieties inside the membrane by hydrophobic interaction. Third, proline residue in linked state does not have free substituent hydrogen to participate in hydrogen bonding of helical structure. The functional consequences of alanine to proline substitution on MTNR1A gene in relation to seasonal reproductive behavior in Chokla ewes deserve future investigations. While (14) it has been founded the most of the polymorphism did not lead to amino acid changes except at position 706, there was a substitution of 'Valine' by 'Isoleucine'. Polyphen-2 analysis was performed on the mutation to assess the potentiality of this mutation, but it was found to be benign, that is lacking any potential damaging effect on the receptor. This study concluded that the SNPs investigated of the MTNR1A gene are good markers for the possibility to decide the Iraqi sheep breeds ability with moderate percentage for out-of-season breeding these genotypes should be taken into account in new genetic selective schemes.

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التغيرات في تشفير جين مستقبل هرمون الميلاتونين MTNR1A في سلالة الاغنام العراقية

محمد عبد الاله رحاوي[1] و احسان حمودي التميمي [2] و نجوى شهاب احمد[3] و احمد علاء الدين العاني[4]

[١]كلية الطب البيطري، جامعة الموصل، [٢]كلية الطب البيطري، جامعة بغداد، [٣]مركز التقنات الاحيائية، جامعة النهرين، العراق ،دائرة البحوث الزراعية وزارة الزراعة .

E-mail: mohammedrahawy@yahoo.com

الخلاصة

إن الهدف من الدراسة الحالية هو الكشف عن تغيرات في تسلسل القواعد النتروجينية المترافق بين تعددالمظاهر للجين مع اي تغيرات في التكرار الاليلي وحدوث طفرات بمواقع لجين مستقبل لهرمون الميلاتونين MTNR1A. اجريت هذه الدراسة في محطة تربية الاغنام التابعة لمركز بحوث المجترات/ بغداد ثم استخلاص الحامض النووي من دم ٦٠ نعجة باستخدام عدة استخلاص من شركة جينيس كجزء كبير من اكسون الثاني للجين عن طريق تضخيمة بواسطة تفاعل سلسلة انزيم البلمرة مع البادي الخاص بالجين. اظهرت النتائج بعد تضخيم بواسطة تفاعل سلسلة انزيم البلمرة ان المنتج من التفاعل للجين مستقبل لهرمون الميلاتونين ظهر بحجم ٨٢٤ زوج قاعدي بعد ترحيله عل الهلام بتركيز ٢%. كما تم ارسال ٢٠ عينة من المنتج من التفاعل للجين مستقبل لهرمون الميلاتونين الى المركز توزيع الوطني للإدارةِ البيئيةِ وبينت نتائج تسلسل القواعد النتروجينية وجود تطابق ١٠٠% مع المستوى القياسي لجنس اغنام أوفسارس للتناسل داخل الموسم ذات الانماط الوراثية rr الذي يمتلك Sequence ID: gb|HQ658147.1| مع عدم وجود تعدد المظاهر للجين في البنك الجينيفيما وجد نسبة تطابق ٩٢% في عينات النعاج ذات الانماط الوراثية RR التي تتناسل خارج الموسم مع وجود ١٩ طفرة وراثية، الا ان خمسة عشر طفرة (G120T, G502C, T512G, T525G, T546A, C567T, T579A, T582C, C605G, A611T, A614T, C620T, G624T, C629T and T642A) يحدث فيها تغير في الحامض الاميني وخاصة تغيرC605G الذي تغير فيه الحامض الاميني برولين الى انلين بينما اربعة طفرات صامتة (G328C, G499C,C604T, C609) بدون تغير الحامض الاميني لذلك يستنتج امكانية التحري عن القطع المفردة لتعدد المظاهر لجين مستقبل هرمون الميلاتونين كدليل جيد لامكانية قدرة الاغنام العراقية للتناسل خارج الموسم التناسلي وكذلك يجب الانتخاب الوراثي الحديث للأنماط الوراثية.

جين، الكلمات المفتاحية: الاغنام العراقية، تعدد المظاهر، جين.