

## Hypothalamus

**Fa fa**

**fa fa**

**Zucker**

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( )

.(Hypothalamus)

( Phospho Signal Transducer and Activator of Transcription)P.STAT3

( Phospho Mitogen-Activated Protein Kinase) PMAPK

Suppressor of Cytokin ) SCSO3

( PhosphoTyrosine Phosphatase 1 B) PTP1B ( Signaling

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**PSTAT3**

**Zucker**

**PMAPK**

**Western Blot**

**Lowry**

**PMAPK**

**PSTAT3**

**.STAT3**

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**Key Words: leptin - resistance - signals - Zucker**

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## Ways of Signals of Leptin Occurring in Fat and Thin Zucker Rats and their Relation with Resistance Mechanism to Leptin

Amal Rakaj\*

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### Abstract

The leptin, which is poly peptides hormones secreted mainly from fat cells, is considered anorexigenic. Leptin inhibits appetite by causing chemical signals after combining with its specific receptors in the hypothalamus area. These signals can be discovered by variation of the concentration of the hypothalamus proteins P.STAT3 (Phospho Signal Transducer and Activator of Transcription) P.MAPK( Phospho Mitogen-Activated Protein Kinase), which can be inhibited by negative feedback of PTP1B( Phospho Tyrosine Phosphatase 1 ) or SCSO3( Suppressor of Cytokine Signaling), resulting in homeostatic and energetic regulation in the body. Moreover, there are signals disorders cases, which lead to obesity in spite of increased plasma level of leptin, which indicates to existence of leptin resistance.

We carried out a study on the variation of P.STAT3 and PMAPK concentration in the hypothalamus area in the obese and lean rats using the Lowry method to measure proteins and western plot to separate the involved proteins in the signals of leptin.

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**There was no difference between two concentration groups of the P.MAPK and also in the kinetic response in the same group. We discovered an important increase in the concentration of the P.STAT3 in lean rats compared with fat rats that are injected by leptin or physiological serum. It can assumed that the mechanism of leptin resistance in fat rats result from the decrease of the concentration of P.STAT3 which could be explained by saturation of leptin receptors in the hypothalamus due to high level of leptin concentration .We found also differences in the kinetic response to leptin in the group of lean rats unlike fat rats in which no difference with the passing of time neither by injecting them with the leptin nor with the physiological serum, which support the hypothesis that the resistance to leptin results from saturation of hypothalamus receptors.**

**Key Word: leptin - resistance - signals - Zucker**

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.( 11 , 12 ,13 )

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(14,15)

.( 16 , 17 , 18)

Type 2

(2)

.(3 , 4 , 5, 6)

(7) Zhang OB

( 11 , 12 , 19 , 20 )

(7, 8 )

AGRP NPY OREXINE

(9) Halaas

MCH

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( 20 URO CORTINE POMC

.(10) (7)

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 ( OB Rb"  
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 " STAT3 " JAK2"  
 ( 8 , 28 , 36 , 37 )  
 ob Re  
 ( 34 , 41 , 42 , 43 , 44 )  
 MAPK / ERK .( 38 )  
 JAK2

STAT3

JAK2

" "

Socs3(45,52,53)

) MAPK

" " STAT3

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(46, 50 , 52,

( 45 , 46 , 47 )

53 , 54 )

MAPK

SHP – I PTPIB

.(JAK2 , 55 ,56 , 57)

.(48,68 )

Socs3

PI3K – PDE3B

– cAMP

( 58 , 59 , 60 , 61 )

JAK2

JAK2

IRS2 (51) IRS1

(62,

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.(81) tyrosine kinase

( 65 , 66 )

64 )

JAK2

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PI3 K

.( 48 ,49 ) PKB ( B )

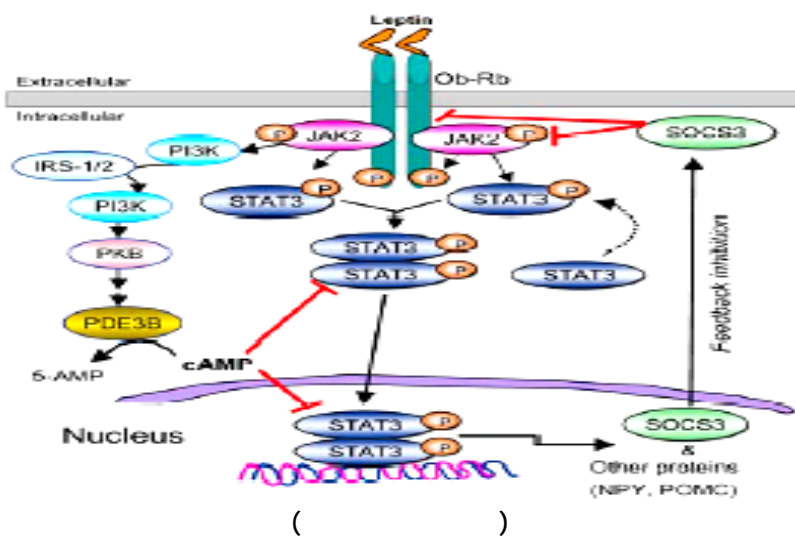
cDNA

Zygot

ObRb

P MAPK P.STAT3

ZUCKER



( from Sahu A. frontiers in Neuroendocrinology 24 "2004 " 225 – 253 )

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Zucker

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cDNA

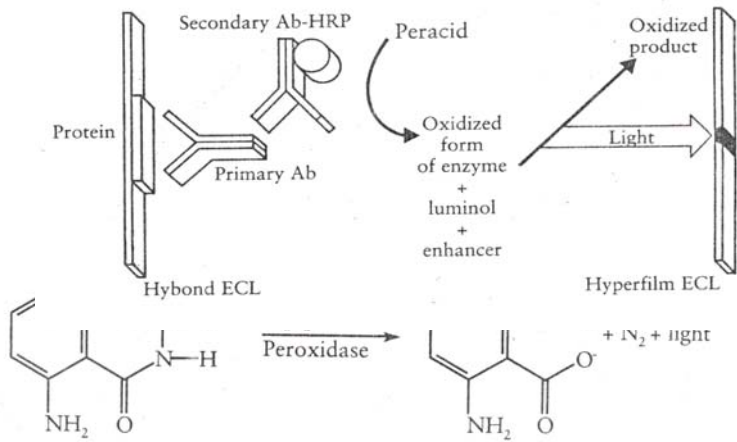


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HRP :  
( horse radish peroxidase)  
HRP spectrophotometer  
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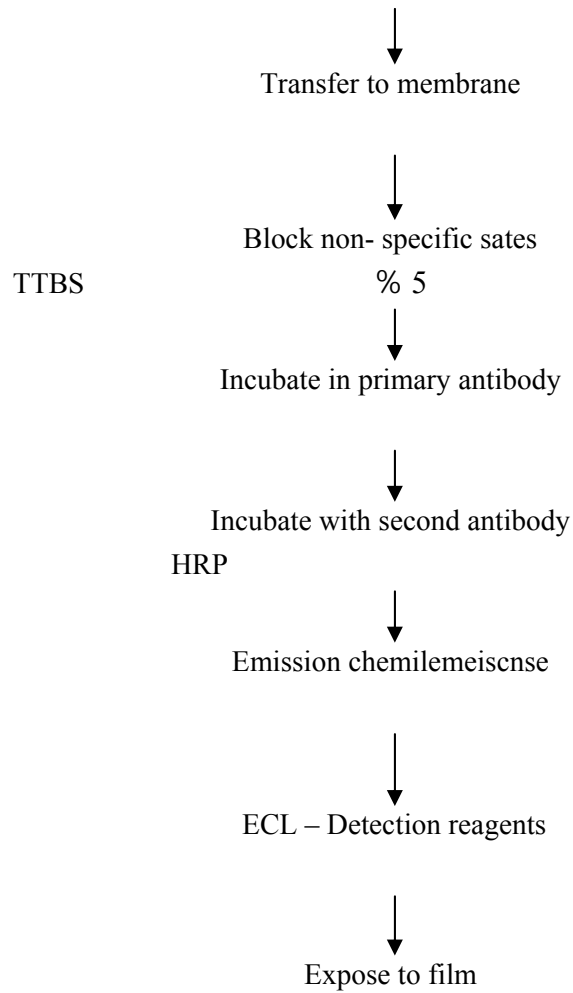
428  
: ( 69 , 70 ) Western Blot

Western Blot



### Western Blot

Separate protein sample by electrophoresis



P.MAPK      PSTAT3      " Euromedex " P. STAT3  
 . Western blot      anticorps mono " "  
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                 6      / 1      anti - IgG  
 (1)      .MAPK      2000

quantity graphical )      1000 / 1      polyclonal  
 ( program image " Sion      anti - IgG  
    5000 / 1

PSTAT3      8 g , sodium chloride " TTBS  
 .(2      )      - 20 ml IM tris HCL dilute to 1000  
                 P.MAPK      ml with distilled water , check PH  
 )      ,7.6 + dilute required volume of  
    PBS Tween 20 : 0.1% tween 20

(3)

P.MAPK  
 50  
 ( 4      ) .      PMAPK(42      PSTAT3 ( 92 KDa  
    - 44 KDa)

Zuker      )

   Hypo thalamus (

   50

   P.MAPK      150

(6 ) .

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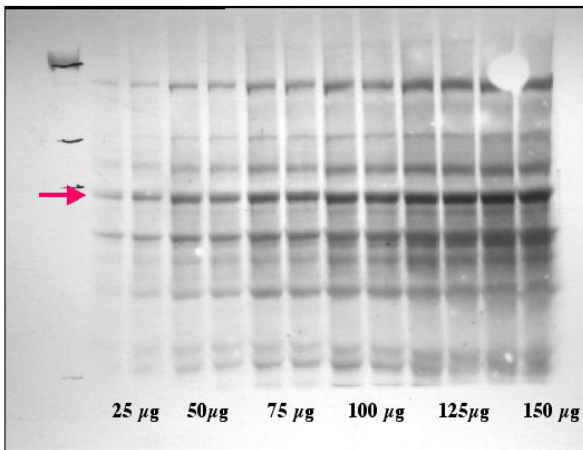
.( 5 )

P.STAT3

PSTAT3

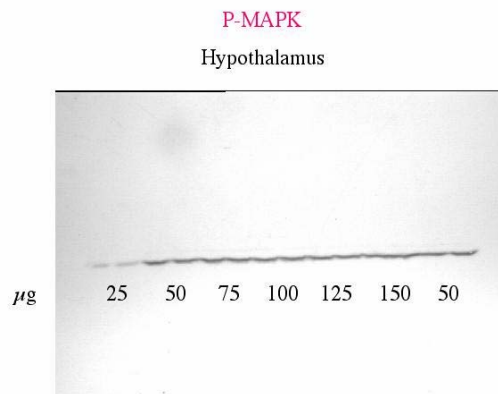
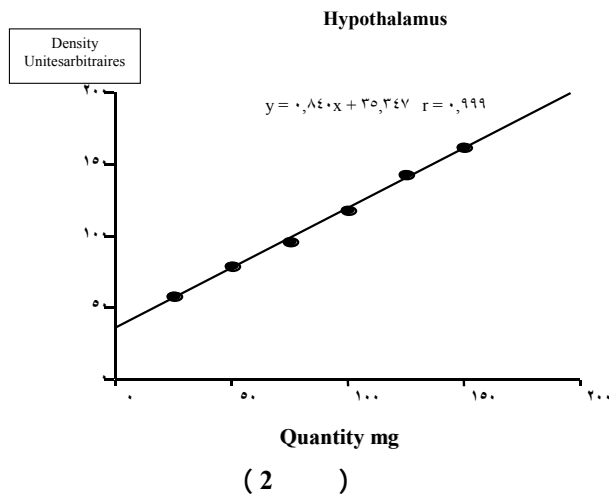
.(6 )

**P-STAT3 Hypothalamus**



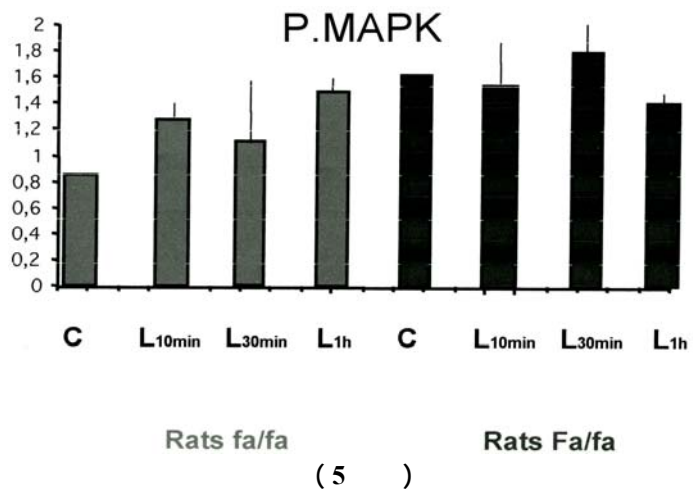
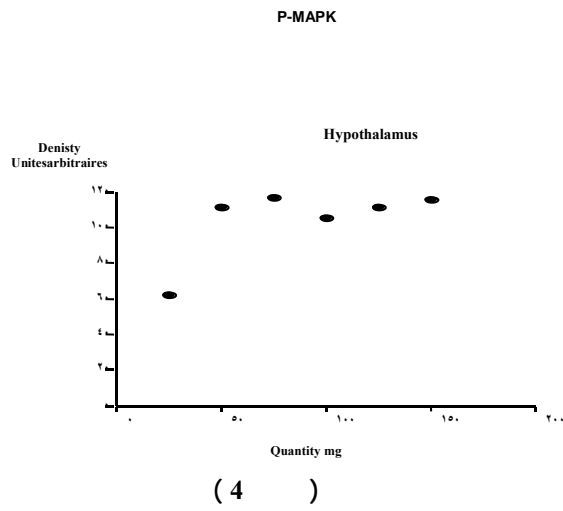
Anti P.STAT3 1 / 1000 in TTBS + 0.1 % milk

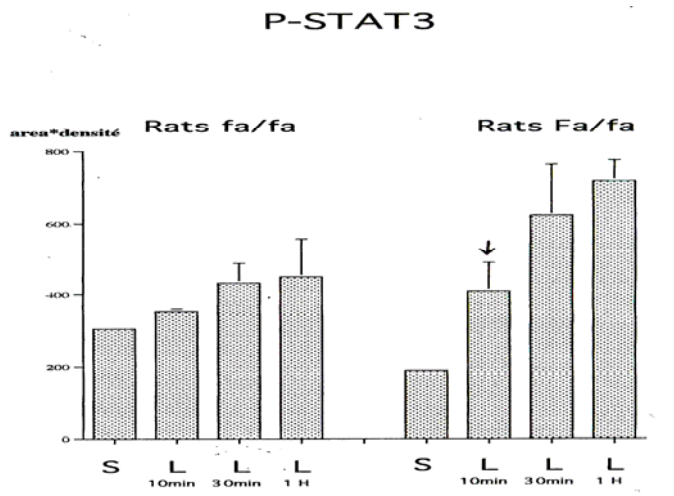
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**Anti P.MAPK 1 / 1000 in TTBS + 0.1 % milk**

**( 3 )**





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31%

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NPYmRNA

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PSTAT3

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PSTAT3

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(16) CARO (76) Banks

P.STAT3

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(80)

P.MAPK

Kim

P.STAT3

Melano stimulin "  $\alpha$  MSH

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melanocorten

(79) Banks

(46 - (54) Wang

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Sco3

STAT3/JAK2

P.

STAT3

" hypothalmus

STAT3 /JAK2

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. P. STAT3

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**list of abbreviation**

**STAT3:** Signal Transducer and Activator of Transcription

**MAPK:** Mitogen-activated Protein Kinase

**JAK:** Janus Kinase

**NPY:** Neuropeptide Y

**AGRP:** Agouti Related Protein

**MCH:** Melanin-Concentrating Hormone

**CRF:** Corticotropin Releasing Factor

**POMC:** Proopiomelanocortin

**IRS:** insulin receptor substrate

**SOCS3:** Suppressor of Cytokine Signaling

**PTP1B:** PhosphoTyrosine Phosphatase 1 B

**SHP1:** SH2-containing Phosphatase-1

**PDE3B :** phosphodiesterase 3B

**Ob-R:** Obese receptor

**DIO :** diet induced obesity

## References

- 1 - Copelman.PG, Obesity as a medical problem. *Nature*. (2000).. 404. 635-643
- 2 -Roth.JM, Halaas.JL Diabetes and obesity. *Diabetes. Metab. Rev.* (1997)..13 (1).1-2.
- 3 – Kennedy . GS The role of depot fat in the hypothalamus control of food intake in the rat, *Proc.R.Soc*(1953) ,579-592
- 4 – Hervey . GR , the effect of lesion in hypothalamus in parabiotic rats ,*J.physiol.*, (1959)145,336-352
- 5 – Hausberger FX parabiosis and transplantation experiments in hereditary obese mice , *Anat.Rec*,(1958), 130-313 (abstrat)
- 6 – Colman DL , obeses and diabetes:two mutant genes causing diabetes obesity syndromes in mice ,*Diabetologie* (1978) 14,141-148
- 7 – Zhang y ,Proenca ,Maffei M ,Barone M ,Leopold L ,et Friedman JM,  
positional cloning of the mouse obese gene and it s human homologue ,  
*Nature*, (1994) 372 ,425-432
- 8 – Chen.H,Charlat.O, Tartaglia.LA, Woolf.EA, Wenig.X, Ellis.SI, Lakey.ND, Culpepper.J, Breitbart.RE, Duyk.GM, Tepper.RT, Morgenstern.JP, Evidence that the diabetes gene encodes th e leptin receptor , identification of a mutation in the leptin receptor gene in db/db mice. *Cell*, (1996), 84 (3) : 491-495
- 9 –Halaas JL,Gajiwala KS ,Maffei M, Cohen SL, Chait GT, Rabinowitz D , Lallone  
RL, Barely SK, Fredman JM,(1995) weight – reducing effects of the plasma protein encoded  
by The obese gene , *Science* , 269: 543-546
- 10 –Halaas .JL, Leptin: A novel hormone secreted by adipose tissue and acting in the cns to regulate energy homeostasis in rodents and humans, these pp 1-120 (umi dissertation services) (1998)
- 11- Kamohara.S, Buecelin.R, Halaas.JL, Frieman.JM, Leptin stimulates uncoupling protin – 2 mRNA expression and krebs cycle activity and inibits lipid synthesis (1999), *Nature*, 380, -374-377
- 12 - Obici.S, Feng.Z, Karkanias.G, Baskin.D.G, , Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats , *Nat. Neurosci*(2002).5. 566-572

- 
- 13 - Liu.L, Karkanias.GB, Murales.JC, Hawkins.M, Barzilia.N, Wang.J, Rossitti.L, J. Biol. Chim, New lessons in regulation of glucose metabolism taught by the glucose 6 phosphatase system – vande Werue etal (1998), 273 : 31160-31167
- 14 - Clement.K, Vaisse. C, Lahlou.N, Cabrol.S, Pelloux.V, Cassuto.D, Gourmelen.M, Dina.C, Champaz.J, Lacorte.JM, Besdevant.A, Bougneres.A, Leboue.Y, Froguel.P, Guy-Grand.B.A, Mutation the human leptin receptor gene caused obesity and pituitary dysfunction, Nature, (1998), 392 : 398:401
- 15 - Montague.C, Farooqi.IS, Whitehead.JP, Soos.MA; Rau.H, Wareham.NJ, SwterCP, Digbi.JE, Mohammed.SN, Hurst.JA, cheetham.CH, Earley.AR, Barnett.AH, Prins.JB, et Orahilly.S, Congenital leptin deficiency is associated with sever early onset obesity in humans, Nature , (1997), 387, 903-908
- 16 - Caro JF, Kolaczynski J W, Nyce MR, Ohannesian JP, Opentanova I, Goldman WH, Lynn RB, Zhang PL, Sinha MK, Considine RV. Decreased cerebrospinal fluid/ serum leptin ratio on obesity : a possible mecanisme for leptin resistance. J. Lancet (1976) 348(9021) : 159-161
- 17 - Carlsson-Lindell.K, Gabelsson.B, Karlsson.C, Bjornason.R, Westphal.O, Carlsson.U, Sjostrom.L, et Carlsson.LMSobese (ob) gene defects are rare in human obesity, Obesity Research, , (1997), 5 , 30-35
- 18 - Considine.RV, Considine.EL, William.CJ, Nyce.MR, Magosin.SA, Baur.TL, Rosata.EL, et Caro.JF, Evidence against either a premature stop codon or the absence of obese gene m RNA in human obesity, J. Clin. Invest, (1995), 95, 2986-2988.
- 19 - Cohen.B, Novick.D, and Rubinstein.M,. Science.Modulation of insulin activites by liptin (1996) 274, 1185-1188.
- 20 - Ahima.RS, Saper.CB, Flier.JS, Elmquist.JK, Leptin regulation of neuroendocrine systems, Frontiers in neuro –endocrinology (2000) , 21, 263-307
- 21 - Rahmouni.K, Haysses.WGLEptin signalling pathways in the central nervous system: interaction between neuro peptide y and melanocortin: Bioessays, (2001), 23 (12) 1095 1099

- 22- Sahu A. Evidence suggesting that GAL melanin concentration hormone (MCH), neurotensine (NT), proopiomelenocortine(POMC) and Y (NPY) are targets of leptin signaling in the hypothalamus. *J.Endocrinology*, (1998) 139(2): 795-809
- 23 - Wang.J, and Leibowitz.KL, , Central insulin inhibit hypothalamic galanin and neuro peptide y gene expression and peptide release in intact rats, *Brain. Res.* (1997) 777, 231-236.
- 24 - Obici.RJ, Fenz.Z, Tan.J, Liu.L, Karkanias.GB, and Rossitti.L., Central melanocortin receptors regulate insuline action, *J,Clin invest*, (2001) 108, 1079-1085
- 25 - Seeley.RJ, Yagaloff.KA, and Fisher.SL, Melanocortin receptors in leptin effects , *Nature* , (1997) 390, 349-350
- 26 - Leibowitz.SF, Wotley.KE , Hypothalamic control of energy balance: differents peptides, differents functions,. *Peptides* (2004), 25, 473-504
- 27 - Halaas J.L, Boozer C, Blair- west J, Fidahusein N, Denton D.A, Freidman J.M  
Physiologica response to long term peripheral and central leptin in lean and obese mice . *Proc. Natl acad sci USA* (1997) 94:8878-8883
- 28 - Tartaglia.LA, Dembskim.M Wing.X, Deng.N, Culpepper.J, Devas.R, Richard.GI, Campfield.LA, Clark.FT, Deeds.J, Muir.C, Sanker.S, Moriarty.A, Moore.KJ, Smutko.JS, Mays.GG, Woolf.EA, Selent-Muro.C, et Tepper.RI, Identification and expression cloning of the leptin receptor ob-R . *Cell*, (1995) 83, 1263-1271.
- 29 - Lin.J, Barb.CR, Matteri.RL, Kraeling.RR, Chen.X, Meinersmann.RJ, et Rampacek.GB, Long form leptin receptor m RNA expression in the brain pituitary, and other tissues in the big. *Domes.Anim. Endocrinol*, (2000) 19 , 53-61.
- 30 - Chung.WK, Power-kehoe.L, Chu.M, Lee.R, et Leibel.RL, Genomic structure of the human OB receptor and identification of two novel intronic microstellites, *Genome.Res*(1996) , 6, 1192 1199.
- 31- Ihle.JN Cytokine receptor signaling *Nature*, (1995), 377, (6550) : 591-594.

- 32 - Ahima.RS, Flier.JS, Leptin, *Annu.Rev,Physiol*, (2000) 62, 413-437
- 33 - Lee.GH, Proenca.R, Montez.JM, Carroll.KM,Darvishzadeh.JG, Lee.JI, et Friedman.JM, Abnormal splicing of the leptin receptor in diabetic mice. *Nature*, (1996) 379, 632-635
- 34 - Tartaglia.LA, the leptin receptor, *J.Biol.Chem*, (1997), 272 , 6093-6096
- 35 - Ghilardi.N et Skoda.RS, The leptin receptor activates janus kinase 2 ans signals for proliferation in a factor –dependent cell line, *Mol, Endocrinol*, (1997), 11, 393-399
- 36 - Emilson.V, Liu.YL, Cawthron.MA, Morton.NM, et Davenpot.M, Expression of the functional leptin receptor m RNA in pancreatic islets and direct inhibitory action of leptin on insulin secretion , *Diabetes*, (1997), 46, 313-316
- 37 - - Laud.K, Gourdou.I, Belair.L, Keisler.DH, et Djian.J. Detection and regulation of leptin receptor m RNA in ovine mammary epithelial cell during pregnancy and lactation . *FEBC, Letters*, (1999),463, : 194-198.
- 38 - Ge.H.F, Huang.L, Pourbahrami.T, and Li.C, *J.Biol. Chem*, generation of soluble leptin receptor by ectodomain shedding of membrane – spanning receptors in vitro and vevo (2002). 277, 45898-45903.
- 39 - Yamashita.T, Murakami.T, Otani.S, Kuwajima.M, Shima.K, Leptin receptor signal transduction : OB Ra and oBRb of fa type, *Biochim. Biophys Res commun* (1998), 246, (3) : 752-759
- 40 - Myer.MG .jr, leptin receptor signaling and the regulation of mammalian physiology. *Recent.Prog. Hormon.Res*, (2004) 59, 287-304.
- 41 - WhiteDW, WangDW, Chua.SC,jr, Morgenstern.JP, Leibel.RL, Baumann.H, Tartaglia.LA, Constitutive and impaired signaling of leptin receptors containing the Gln  
□ pro extra cellular domain fatty mutation. *Proc.Nat L Acad Sci USA*, (1997) ,94, 10657-10662.
- 42 - Darnell.JE, Stats and gene regulation . *Science*. (1997). 277 (5332) : 1630-1635.
- 43 - Harvey.J, Shford.MLJA, Leptin in the CNS: much more than a satiety signal *Neuropharmacology* , (2003) 44 , 845-854



- 44 - Kloek.C, Haq.AK, Dunn.SL, Lavery.HJ, Banks.AS, Myers M G jr , Regulation of jak kinase by intracellular leptin receptor sequence: *J.Biol.Chem* , (2002), 277, :41547-41555.
- 45 - Banks.AS, Davis.SM, and Bates.SH, *J.Biol-Chem*, (2000) 275, 14563-14572.
- 46 - Bjorback.C, Elmquist.JK, Frantz.JD, Shoelson.SE, Flier.JS, Identification of socs3 as a potential mediator of central leptin resistance , *Mol.Cell* 1 (4) :A chimeric luciferase reporter system. *Arrow* , indicates leptin receptor ( 80 Kda ) application reference (1998) 619-625
- 47 - Murakami.T, Yamashita.T, Iida.M, Kuwajima.M, Shima.K, A short form of leptin receptor performs signal transduction. *Biochim.Biophys.Res. Commun* , (1997). 231(1); 26-29.
- 48 - Saltiel.AR, and Pessin.JE, Insulin signaling pathways in time and space, *Trends, Cell. Biol*, (2002), 12, 65-71
- 49 - Niswender.KD , Morton.GJ and Steans.WH, Intracellular signaling key enzyme in leptin -induced , anorexia. *Nature* (2001), 413, 794-795.
- 50 - Bates.SH, Steans.WH, and Schubert.M, Stat3 signaling is required for leptin regulation of energy balance but not reproduction . *Nature*, (2003), 421, 856-859
- 51 - Dupon.J, Derouet.M, Simon.J, and Taouis.M, Effect of nutritional state on the formation of complex involving insulin receptor, IRS-1, the 52 Kda Src homology/collagen protein Shc isoform and phosphatidylinositol3-Kinase activity . *Biochem, J*; (1998), 335, 293-300
- 52 - Bjorbaek.C, Lavery.HJ, and Bates.SH, SOS3 mediates feed back inhibition of the leptin receptor via tyr985 , *J,Biol, Chem*, (2000), 275, 293-300.
- 53 - Bjorbaek.C, EL-Haschimi.K, Frantz.JD, Flier.JS, The role of SOS3 in leptin signaling and leptin resistance, *J. Biol-Chem*, (1999) 274,(42), 30059-30065.
- 54 - Wang.Z, Zhou.YT, Kakkuma.T, Lee.Y, Kalra.PS, Pan .W, Unger.RH, Leptin resistance of adipocytes in obesity : role of cytokine signaling. *Biochem. Biophys. Res. Commun* oct 14 (2000), 277 (1): 20-26.

- 
- 55- Zabolotny.JM, Bence-Hanule.CKK, Stricker-Krongrand.A, Haj.F, Wang.Y, Minokoshi.Y, Kim.YB, Elmquist.JK, Tartaglia.LA, Kahn.BB, Neel.BG, PTP 1 regulates leptin signal transduction in vivo , *Dev.Cell*, (2002), 2, 489-495.
- 56 - Cheng.A, Uetani.N, Simoncic.PD, Chaubey.VP, Lee-Loy.A, McGlade.CJ, Kennedy.BP, Tremblay.ML, Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase1B, *Dev.Cell*, (2002), 2, 497-503.
- 57 - Carpenter.LR, Farruggella.TJ, Symes.M, Karow.ML, Yancopoulos.GD, Stahl.N. Enhancing leptin reponse by preventing SH-containing phosphatase 2 Interaction with ob receptor . *Proc. Natl. Acad. Sci. USA*. (1998). 95. (11). 6061-6066.
- 58 - Kalra.SP, Dube.MG, Pu.S, Xu.B, Horvath.TL, Kalra.PS, Interacting appetite – regulating pathways in the hypothalamic regulation of body weight, *Endocr. Rev*, (1999), 20, 68-100.
- 59 - Schartz.MW, Woods.SC, Porte.D,jr, Seely RJ, Baskin.DG Central nervous system control of food intake, *Nature*, (2000) 404: 661-671.
- 60 - Campfield.LA, Smith.FJ, Guisez.Y, Devos.R, Burn.P, Recombinant mouse OB protein : evidence for a peripheral signal linking adiposity and central neural networks , *Science*, (1995), 269, (5223) : 546;
- 61 - Sahu.A, Leptin signaling in the hypothalamus emphasis on energy homeostasis and leptin resistance , *Front neuro endocrinol*, (2004) , 24, 225-253.
- 62 - Ruth.M, Seeber.J, Smith.T, Waddel.BJ, Plasma leptin binding activity and hypothalamic leptin receptor expression during pregnancy and lactation in the rats *Biology of Reproduction* , (2002), 66, 1762-1767.
- 63 - Laydman.SR, and Grattan.DR, Lagrosses entraine une sorte de resistance a la leptin , *Endocrinologie as doi* (2004) , 10, 1210, -0338.
- 64 - Friedman.JM, and Halaas.JL, leptin and the regulation of body weight in mammals. *Nature*, (1998), 395, 763-770.
- 65 - Considine.RV, Sinha.MK, Heiman.ML, Karianciunes.A, Stephans.TW, Nyce.MR, Ohannesian.JP, Marco.CC, McKee.LJ, BauerTL, et all b, Serum immuno reactive –leptin concentration in normal- weight and obese human , *M,Engl.J.Med*, (1996) 334, 292-295

- 66 - O Ralhill.S, Farooqi.IS, Yeog.S Challis.BG, minirevu: Human obesity –lessons from monogenic , Disorder. *Endocrinology* , (2003) 144 : 3757\_3764.
- 67 - Wang.MY, Zhou.YT, New, gard.CB, Unger.RH, Anovel leptin receptor isoform in rat, *FEBS,Lett*, (1996), 392 (2) 87-90
- 68 - Niswender KD, Gallis.B, Blevins.JE, Corson.MA, Schwartz.WM, Baskin.DG, Immunocytochemical detection of phosphotidylinositol3-kinase activation by isulin and leptin , *J, Histochem.Cytochem .* (2003) 51(3): 275-283
- 69 – Andrews, A. T.. *electrophoresis: thepry, Technique and biochemical and clinical application* , second edition in monographs on physical biochemistry, edited by A. R peacock and W.R.Harrington, Oxford science puplication, ( 1968 ) .
- 70 - Johnstone, A. and thorpe, R.,*Immunochemistry in practice*, Blackwell science pupulation, (1982 ) .
- 71 - Maffei.M, Halaas.J, Ravussin .E, Pratley.R.E, Lee G.H, Zhang .Y, Fei.H; Kim.S, Lallon.R, Ranganathan.S, and Al. Leptin level in human rodent: measurement of plasma leptin and ob RNA in obeses and weight-reduced subjects. *Nat.Med.* ( 1995 ) , 1, 1155-1161.
72. Iida.M,Murakami.T, Ishida.K, Mizuno.A, Kuwajima.M, Shima.K, Subtitution at codon 269 (glutamine→proline) of the leptin receptor (OB-R)cDNA in the only mutation found in Zucker fatty (fa/fa) rats. *Biochim. Biophys.res.commun.* (1996).224(2): 597-604.
73. Guerre-Millo.M, Regulation of gene and over expression in obesity. *Biomed. Pharma Cother.* (1997). 51(8) : 318-323.
- 74 . Levin.B.E, Dunnmeynell.A.A, Reduced central leptin sensitivity in rats with diet-induced obesity. *Am. J. Physiol. Regul. Intgr. Comp. Physiol;* (2002) , 283. R941-R948.
75. El – Haschimi .K, Pierroz .DD, Hileman S.M, Bjorbaek.C, Flier.J.S, Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. *J.Clin.Invest.* ( 2000) 105 (12) : 1827-1832
76. Banks.WA. : Is obesity is decrease of the blood- brain barrier. *Physiologic, pathological and evolutionary considerations.* *Curr.pharm.Design.* (2003 ) 9 : 801-809

- 
77. Heymsfield SP, Geenberg AS, Fujioka k, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane , Self B, Hunt P, Mc Camish M. Recombinant leptin for weight loss in obesoes and lean adult a randomised, controlled-dose escalation trial. J. JAMA (1999) 282 (16) : 1568-1575
78. Pal.R, Sahu .A. Leptin signaling in the hypothalamus during central leptin infusion. Endocrinology (2003). 144 : 3789-3798.
79. Banks .W.A, The many live of peptides. (2004) . 25 : 331-338
80. Kim, Y.B., uotami,S., pierroz, D.D., flier, J.S. and kahn, B.B. Endocrinology Adipocyte – selective reduction of the leptin receptor induced by antisense RNA leads to increased adiposity (2000)141 , 2328-2339 .
- 81- Szanto.I, and Khan.CR, Selective intraction between leptin and insulin signaling pathways in hepatic cell line , Proc.Natl,Acad.Sci.USA. (2000), 97, 2355-2360
- 82-Levin.B.E, Dunnmeynell.A.A, Dysregulation of arcuate nucleus preproneuropeptide YmRNA in diet –induced obesoes rats . Am.J.Physiol . (1997). 272. R 1365-1370

.2005/12/28 :

.2006/5/22 :