



Open Access

REVIEW

Leptin and its actions on reproduction in males

Ifrah Alam Malik¹, Damayanthi Durairajanayagam¹, Harbindar Jeet Singh^{1,2}

Leptin, an adipocyte-derived hormone, serves numerous physiological functions in the body, particularly during puberty and reproduction. The exact mechanism by which leptin activates the gonadotropin-releasing hormone (GnRH) neurons to trigger puberty and reproduction remains unclear. Given the widespread distribution of leptin receptors in the body, both central and peripheral mechanisms involving the hypothalamic-pituitary-gonadal axis have been hypothesized. Leptin is necessary for normal reproductive function, but when present in excess, it can have detrimental effects on the male reproductive system. Human and animal studies point to leptin as a link between infertility and obesity, a suggestion that is corroborated by findings of low sperm count, increased sperm abnormalities, oxidative stress, and increased leptin levels in obese men. In addition, daily leptin administration to normal-weight rats has been shown to result in similar abnormalities in sperm parameters. The major pathways causing these abnormalities remain unidentified; however, these adverse effects have been attributed to leptin-induced increased oxidative stress because they are prevented by concurrently administering melatonin. Studies on leptin and its impact on sperm function are highly relevant in understanding and managing male infertility, particularly in overweight and obese men.

Asian Journal of Andrology (2019) 21, 296–299; doi: 10.4103/aja.aja_98_18; published online: 11 December 2018

Keywords: leptin; male infertility; obesity; spermatozoa; sperm DNA fragmentation

INTRODUCTION

Leptin, a 16-kDa nonglycosylated peptide hormone consisting of 167 amino acids, is a product of the obese (*ob*) or leptin (*LEP*) gene on chromosome 6 in mice and chromosome 7 in humans.¹ It was discovered in 1994 through positional cloning of the mouse gene² and is mainly synthesized and secreted constitutively by white adipose tissue.³ Small quantities of leptin are also secreted by the gastric mucosa,⁴ mammary epithelial cells,⁵ placenta,⁶ anterior pituitary gland,⁷ myocytes,⁸ human spermatozoa,⁹ ovaries, lymphoid tissue, and bone marrow.¹⁰

Leptin acts by binding to its receptors,¹¹ which are widely distributed in the hypothalamus,¹² pancreas, testes,¹³ ovaries,¹⁴ skeletal muscles,¹⁵ kidneys, lungs,¹⁶ and even on the tails of spermatozoa.¹⁷ These receptors, often denoted as leptin receptor (OBR or LEPR), belong to the class 1 cytokine receptor family.¹⁸ To date, six leptin receptor isoforms have been identified: OBR^a–OBR^f. Based on their structure, the isoforms are divided into long, short, or soluble types. The long form is responsible for the isoform's cellular actions, the short form is responsible for its transport across the cell membrane and blood–brain barrier, and the soluble form aids its transport in the circulation.¹⁸ After binding to its receptor, leptin activates several signaling pathways, including the Janus kinase-signal transducer and activator of transcription (JAK-STAT), 5' adenosine monophosphate-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), phosphoinositide 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) signaling pathways,^{19,20} depending on the target cell type.

Serum leptin levels are positively correlated with body fat percentage. The levels are generally higher in women than in men,

even when matched for body mass index (BMI).^{21–23} These differences may either be due to a higher percentage of body fat mass in women or to the stimulatory effects of estrogen and progesterone. Interestingly, 17 β -estradiol increases leptin secretion in adipose tissue cultures from women but not from men.^{24,25} In children, serum leptin levels increase progressively with age until puberty in both girls and boys. After puberty, serum leptin levels in boys either remain unchanged or decrease slightly. This might be due to testosterone's effect on body composition in men. Body fat in men generally decreases as muscle mass increases following puberty. Additionally, testosterone may inhibit leptin production in the adipose tissue.²⁶

Leptin has both central and peripheral effects in the body as indicated by the widespread distribution of its receptors. Some of these effects include regulating food intake and body weight,²⁷ modulating the hypothalamic–pituitary–thyroid^{28,29} and hypothalamic–pituitary–growth hormone axes,^{30,31} cartilage growth and bone formation,^{32,33} proliferation of vascular smooth muscle cells,^{34,35} immunity, inflammation,^{36,37} and reproduction.

LEPTIN AND REPRODUCTION

Leptin plays an important role in pubertal development and fertility, more so in women. Mice lacking the leptin gene (*ob/ob* mice) are infertile.³⁸ Gonadotropin levels are lower in both male and female *ob/ob* mice, although the gonadotrophs in these mice have been shown to respond adequately when challenged with gonadotropin-releasing hormone (GnRH).³⁹ Testes and ovaries in leptin-deficient mice are smaller with several morphological and biochemical abnormalities compared to those of age-matched wild-type control mice. In addition, seminiferous tubules of leptin-deficient mice contain fewer sperm than

¹Department of Physiology, Faculty of Medicine, Universiti Teknologi MARA, Sungai Buloh Campus, Sg Buloh 47000, Selangor, Malaysia; ²1-PPerForM, Universiti Teknologi MARA, Sungai Buloh Campus, Sg Buloh 47000, Selangor, Malaysia.

Correspondence: Dr. HJ Singh (hjsingh@salam.uitm.edu.my)

Received: 02 May 2018; Accepted: 21 October 2018

those of their wild-type littermates, and their Leydig cells are smaller with less cytoplasmic content.⁴⁰ Leptin treatment restores fertility in *ob/ob* mice.⁴¹

Leptin is believed to initiate puberty by triggering the nocturnal gonadotropin surges associated with puberty. Appropriate energy stores must be attained before reproduction commences, particularly in women. Serum leptin levels, which correlate positively with body fat percentage, provide the required information on energy status to the hypothalamus. Whether the same is true in males is uncertain. The exact mechanism by which leptin triggers GnRH neurons to secrete gonadotropins remains uncertain. GnRH neurons are devoid of leptin receptors; therefore, stimulation of gonadotropins by leptin must involve another indirect pathway. In this regard, the role of kisspeptin neurons has been proposed; however, kisspeptin neurons appear to contain few leptin receptors⁴² and therefore may not trigger GnRH release. The other possibility is the premammillary nucleus (PMN). Cells in the PMN have been shown to express abundant leptin receptors, and PMN has projections on both kisspeptin and GnRH neurons.⁴³ Thus, leptin may stimulate the PMN, which in turn excites the GnRH neurons, both directly and possibly through the kisspeptin neurons, to release the gonadotropins.⁴⁴

Other possible mechanisms of action of leptin on GnRH neurons have been suggested. Several hypothalamic neuropeptides, including pro-opiomelanocortin (POMC) and cocaine-and-amphetamine-regulated transcript (CART), stimulate GnRH neurons, both of which are stimulated by leptin. Neuropeptide Y (NPY) and agouti-related peptide (AgRP) inhibit the GnRH neurons, and secretion of these peptides is inhibited by leptin.⁴⁵ Removal of AgRP- or NPY-producing neurons, either by ablation or gene knockout, resurrects partial fertility in leptin-deficient mice.⁴⁶ Several of these neurons act together with kisspeptin/neurokinin B/dynorphin (KNDy) neurons, which are upstream regulators of GnRH secretion.⁴⁷ In addition, studies also suggest that leptin acts at different levels of the pituitary–testicular axis in males⁴⁸ to exert its effects on the male reproductive organs. The presence of leptin receptors in the seminiferous tubules and seminal plasma⁴⁹ on the Sertoli and Leydig cells suggests that leptin may also have a direct role in spermatogenesis and endocrine function of the testes.^{50–52}

LEPTIN AND MALE INFERTILITY

While leptin is necessary for normal sexual maturation and function, corroborative evidence from human and animal studies suggests that, when in excess, leptin may detrimentally affect sperm parameters. Serum leptin levels correlate positively with the percentage of body fat or BMI. Males with high BMI have low total sperm counts,^{53–57} decreased sperm motility,⁵⁵ and increased sperm DNA fragmentation.^{57,58} They also have significantly higher levels of estradiol and luteinizing hormone and lower levels of testosterone than normal-weight males.^{56,59,60} A case–control study on 42 obese and nonobese men found that obese men with high leptin levels, in addition to having low sperm concentrations and vitality and higher sperm DNA fragmentation, had higher sperm mitochondrial membrane potential than normal-weight men.⁶¹ Male Wistar rats fed with a high-fat diet over different time periods had increased body weight that correlated positively with serum leptin levels but had lower sperm motility.⁶² A more recent study that further substantiated leptin's role in male infertility found that male Wistar rats treated with leptin for 42 days had significantly decreased fertility potential and increased preimplantation embryo loss after artificial insemination *in utero*.⁶³ These findings from human and

animal studies suggest that leptin might be the link between poor sperm parameters and obesity.

Adipocytes produce numerous adipokines that signal the functional status of the adipose tissue to targets in the brain and other tissues. Secretion of some of these, including leptin, adiponectin, fibroblast growth factor 21 (FGF21), retinol-binding protein 4 (RBP4), bone morphogenetic protein (BMP)-4, BMP-7, dipeptidyl peptidase 4 (DPP-4), apelin, chemerin, resistin, vaspin, tumor necrosis factor- α (TNF- α), and progranulin, is altered in obese individuals and is believed to contribute to several obesity-associated diseases. Some adipokines, such as leptin, are pro-inflammatory, while others are anti-inflammatory. However, except for leptin, little is known about their impact on sperm function and reproduction.

An *in vitro* study examining the effect of leptin on mature ejaculated human sperm found no difference in the motility and capacitation ability of sperm after either 3 h or 24 h of incubation;⁶⁴ however, recent studies *in vivo* have shown that leptin adversely affects rat sperm. Sprague-Dawley rats given single-daily intraperitoneal injection of leptin, in doses ranging from 5 to 30 $\mu\text{g kg}^{-1}$ body weight for 6 weeks, had significantly lower sperm count, higher fraction of sperm with abnormal morphology. In addition, they also had lower seminiferous tubular epithelial height and diameter than normal age-matched rats.⁶⁵ Neither serum leptin levels nor body weight differed significantly between the controls and leptin-treated rats in this study. The reason for this lack of difference in serum leptin concentration and body weight is unclear but might be attributed to leptin's short half-life, which is 9–12 min in the circulation. Leptin was administered as a single daily dose in this study, and blood samples were collected 24 h after the last dose to measure leptin and other hormones.⁶⁵ These findings were confirmed by another research group using similar leptin doses with a similar study design.⁶⁶ A more recent study using 60 $\mu\text{g kg}^{-1}$ body weight of leptin also reached the same conclusions.⁶⁷ Researchers in the latter studies also found evidence of increased reactive oxygen species (ROS)⁶⁶ levels, high 8-hydroxy-2-deoxyguanosine (8-OHdG) levels, and increased sperm DNA fragmentation^{67,68} after administering leptin. Incidentally, leptin has been shown to induce ROS formation in phagocytic^{69,70} and nonphagocytic^{71,72} cells and in renal tubular cells by activating nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidase.⁷³ Thus, leptin may increase sperm damage by generating ROS in the seminiferous tubular cells or in the epididymis. That oxidative stress might indeed be involved is also supported by findings that these adverse effects of leptin are prevented by concurrent administration of melatonin, a very powerful antioxidant.⁶⁸

ROS can either positively or negatively impact sperm function depending on the nature, concentration, location, length of exposure, and exposure to environmental factors such as temperature, ions, proteins, and ROS scavengers.⁷⁴ At physiological levels, ROS play significant roles in sperm maturation, capacitation,⁷⁵ and acrosome reaction.⁷⁶ At pathological levels, ROS impair testicular germ cell proliferation,⁷⁷ negatively impact sperm plasma membrane fluidity,⁷⁴ impair sperm motility,⁷⁸ and increase sperm DNA damage.⁷⁹ Infertile men with high ROS levels tend to have more sperm with abnormal morphology.⁸⁰ ROS have also been associated with increased apoptosis in sperm samples.⁸¹ The somewhat higher susceptibility of spermatozoa to ROS attack may be because the sperm have less cytoplasm than somatic cells⁸² and the spermatid cell membrane is rich in polyunsaturated fatty acids.^{82–84}

While high leptin levels evidently increase oxidative stress and consequently adversely affect the sperm, the precise mechanisms and pathways in the testes and sperm remain unclear. However, one of the

many leptin-signaling pathways may be involved. Of the five pathways mentioned herein, those related to oxidative stress are the AMPK, PI3K, MAPK, and mTOR pathways. These pathways have well-established roles in leptin's mode of action.¹⁹ Microarray analysis of the testes from leptin-treated Sprague-Dawley rats in our laboratory showed a 2-fold upregulation in the expression of genes associated with these pathways (unpublished data). Additionally, our preliminary study in which leptin was concurrently administered with either a PI3K inhibitor (LY294002) or an AMPK pathway inhibitor (dorsomorphin) found that the PI3K inhibitor prevented leptin's adverse effects on sperm, while the AMPK inhibitor did not.⁸⁵ Leptin's action on these pathways and their roles in leptin's adverse effects require further study.

The effects of leptin on sperm count and morphology are reversible. Nearly all sperm parameters that were affected by 6 weeks of leptin treatment (60 µg kg⁻¹ body weight) returned to levels that were similar to those of age-matched controls by 8 weeks after stopping the treatment.⁶⁷ The time required for the parameters to normalize after leptin treatment suggests that leptin's effects may occur somewhere upstream in spermatogenesis and may not involve the spermatogonia or the matured sperm.

CONCLUSIONS

Since its discovery, leptin has been shown to have significant roles in numerous physiological functions, including reproduction. The widespread presence of leptin receptors throughout the body supports its pleiotropic role. However, recent studies suggest that increased leptin levels may have detrimental effects. Serum leptin levels are closely associated with body fat percentage and weight. Obesity is associated with numerous lifestyle diseases and is often considered a contributing factor to male infertility. Although adipocytes also produce many other adipokines, studies suggest that leptin may be an important link between obesity and obesity-related diseases. In this regard, leptin administration has been shown to increase blood pressure in pregnant and nonpregnant female rats, increase urinary protein excretion, interfere with glucose metabolism, and activate endothelial cells.^{86,87} When administered to nonobese male rats, leptin decreases sperm count and increases sperm abnormalities. Current evidence suggests that most of these effects on sperm are due to leptin's ability to increase oxidative stress because markers of DNA damage due to oxidative stress increase in the sperm after administering leptin. In addition, these effects are prevented by concurrently administering melatonin. Though the effects of oxidative stress on sperm function have been well established, the exact mechanism through which leptin exerts these effects is uncertain and awaits further study. More importantly, leptin's role in infertility in obese males must be considered. Understanding the mechanisms involved in leptin's effects on sperm parameters and function may improve the management of obesity-associated infertility in males.

AUTHOR CONTRIBUTIONS

IAM wrote the manuscript. DD helped revise the manuscript. HJS helped prepare, revise, and review the manuscript critically for accurate intellectual content. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

ACKNOWLEDGMENTS

Some of the work from our laboratory that is cited in the text was supported by grants from the Fundamental Research Grant Scheme, FRGS 600-RMI 1/2010 and FRGS 600-RMI/FRGS 5/3 (0011/2016).

REFERENCES

- Isse N, Ogawa Y, Tamura N, Masuzaki H, Mori K, *et al*. Structural organization and chromosomal assignment of the human obese gene. *J Biol Chem* 1995; 270: 27728–33.
- Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, *et al*. Positional cloning of the mouse *obese* gene and its human homologue. *Nature* 1994; 372: 425–32.
- Masuzaki H, Ogawa Y, Isse N, Satoh N, Okazaki T, *et al*. Human obese gene expression. Adipocyte-specific expression and regional differences in the adipose tissue. *Diabetes* 1995; 44: 855–8.
- Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, *et al*. The stomach is a source of leptin. *Nature* 1998; 394: 790–3.
- Smith-Kirwin SM, O'Connor DM, De Johnston J, Lancey ED, Hassink SG, *et al*. Leptin expression in human mammary epithelial cells and breast milk. *J Clin Endocrinol Metab* 1998; 83: 1810–3.
- Singh HJ, Abu Bakar A, Che Romli A, Nila A. Raised leptin concentrations in fetoplacental tissues from women with preeclampsia. *Hypertens Pregnancy* 2005; 24: 191–9.
- Jin L, Burguera BG, Couce ME, Scheithauer BW, Lamsan J, *et al*. Leptin and leptin receptor expression in normal and neoplastic human pituitary: evidence of a regulatory role for leptin on pituitary cell proliferation. *J Clin Endocrinol Metab* 1999; 84: 2903–11.
- Wang J, Liu R, Hawkins M, Barzilai N, Rossetti L. A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. *Nature* 1998; 393: 684–8.
- Aquila S, Gentile M, Middea E, Catalano S, Morelli C, *et al*. Leptin secretion by human ejaculated spermatozoa. *J Clin Endocrinol Metab* 2005; 90: 4753–61.
- Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, *et al*. Leptin in human physiology and pathophysiology. *Am J Physiol Endocrinol Metab* 2011; 301: E567–84.
- Gorska E, Popko K, Stelmaszczyk-Emmel A, Ciepiela O, Kucharska A, *et al*. Leptin receptors. *Eur J Med Res* 2010; 15 Suppl 2: 50–4.
- Houseknecht KL, Portocarrero CP. Leptin and its receptors: regulators of whole-body energy homeostasis. *Domest Anim Endocrinol* 1998; 15: 457–75.
- Kieffer TJ, Heller RS, Habener JF. Leptin receptors expressed on pancreatic beta-cells. *Biochem Biophys Res Commun* 1996; 224: 522–7.
- Abir R, Ao A, Jin S, Barnett M, Raanani H, *et al*. Leptin and its receptors in human fetal and adult ovaries. *Fertil Steril* 2005; 84: 1779–82.
- Guerra B, Santana A, Fuentes T, Delgado-Guerra S, Cabrera-Socorro A, *et al*. Leptin receptors in human skeletal muscle. *J Appl Physiol* 2007; 102: 1786–92.
- Sharma K, Considine RV. The Ob protein (leptin) and the kidney. *Kidney Int* 1998; 53: 1483–7.
- Jope T, Lammert A, Kratzsch J, Paasch U, Glander HJ. Leptin and leptin receptor in human seminal plasma and in human spermatozoa. *Int J Androl* 2003; 26: 335–41.
- Singh HJ. The physiology of leptin: revisited. *Med Health Rev* 2009; 1: 92–134.
- Kwon O, Kim KW, Kim MS. Leptin signalling pathways in hypothalamic neurons. *Cell Mol Life Sci* 2016; 73: 1457–77.
- Fruhbeck G. Intracellular signalling pathways activated by leptin. *Biochem J* 2006; 393: 7–20.
- Schrauwen P, van Marken Lichtenbelt WD, Westerterp KR, Saris WH. Effect of diet composition on leptin concentration in lean subjects. *Metab Clin Exp* 1997; 46: 420–4.
- Al-Sultan AI, Al-Elq AH. Leptin levels in normal weight and obese Saudi adults. *J Fam Med Community Health* 2006; 13: 97–102.
- Kazmi A, Sattar A, Hashim R, Khan SP, Younus M, *et al*. Serum leptin values in the healthy obese and non-obese subjects of Rawalpindi. *J Pak Med Assoc* 2013; 63: 245–8.
- Shimizu H, Shimomura Y, Nakanishi Y, Futawatari T, Ohtani K, *et al*. Estrogen increases *in vivo* leptin production in rats and human subjects. *J Endocrinol* 1997; 154: 285–92.
- Casabiell X, Pineiro V, Peino R, Lage M, Camina J, *et al*. Gender differences in both spontaneous and stimulated leptin secretion by human omental adipose tissue *in vitro*: dexamethasone and estradiol stimulate leptin release in women, but not in men. *J Clin Endocrinol Metab* 1998; 83: 2149–55.
- Garcia-Mayor RV, Andrade MA, Rios M, Lage M, Dieguez C, *et al*. Serum leptin levels in normal children: relationship to age, gender, body mass index, pituitary-gonadal hormones, and pubertal stage. *J Clin Endocrinol Metab* 1997; 82: 2849–55.
- Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, *et al*. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. *Nature* 2001; 411: 480–4.
- Paz-Filho G, Delibasi T, Erol HK, Wong ML, Licinio J. Congenital leptin deficiency and thyroid function. *Thyroid Res* 2009; 2: 11.
- Mantzoros CS, Ozata M, Negrao AB, Suchard MA, Ziotopoulou M, *et al*. Synchronicity of frequently sampled thyrotropin (TSH) and leptin concentrations in healthy adults and leptin-deficient subjects: evidence for possible partial TSH regulation by leptin in humans. *J Clin Endocrinol Metab* 2001; 86: 3284–91.
- Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, *et al*. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 1998; 392: 398–401.
- Gat-Yablonski G, Phillip M. Leptin and regulation of linear growth. *Curr Opin Clin Nutr Metab Care* 2008; 11: 303–8.



- 32 Idelevich A, Sato K, Baron R. What are the effects of leptin on bone and where are they exerted? *J Bone Miner Res* 2013; 28: 18–21.
- 33 Gonnelli S, Caffarelli C, Nuti R. Obesity and fracture risk. *Clin Cases Miner Bone Metab* 2014; 11: 9–14.
- 34 Schinzari F, Tesauro M, Rovella V, Di Daniele N, Mores N, *et al*. Leptin stimulates both endothelin-1 and nitric oxide activity in lean subjects but not in patients with obesity-related metabolic syndrome. *J Clin Endocrinol Metab* 2013; 98: 1235–41.
- 35 Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Adiposity, adipokines, and risk of incident stroke in older men. *Stroke* 2013; 44: 3–8.
- 36 Iikuni N, Lam QL, Lu L, Matarese G, La Cava A. Leptin and inflammation. *Curr Immunol Rev* 2008; 4: 70–9.
- 37 Batra A, Okur B, Glauben R, Erben U, Ihbe J, *et al*. Leptin: a critical regulator of CD4⁺ T-cell polarization *in vitro* and *in vivo*. *Endocrinology* 2010; 151: 56–62.
- 38 Martins AD, Moreira AC, Sa R, Monteiro MP, Sousa M, *et al*. Leptin modulates human Sertoli cells acetate production and glycolytic profile: a novel mechanism of obesity-induced male infertility? *Biochim Biophys Acta* 2015; 1852: 1824–32.
- 39 Batt RA, Everard DM, Gillies G, Wilkinson M, Wilson CA, *et al*. Investigation into the hypogonadism of the obese mouse (genotype ob/ob). *J Reprod Infertil* 1982; 64: 363–71.
- 40 Mounzih K, Lu R, Chehab FF. Leptin treatment rescues the sterility of genetically obese *ob/ob* males. *Endocrinology* 1997; 138: 1190–3.
- 41 Kiess W, Blum WF, Aubert ML. Leptin, puberty and reproductive function: lessons from animal studies and observations in humans. *Eur J Endocrinol* 1998; 138: 26–9.
- 42 Louis GW, Greenwald-Yarnell M, Phillips R, Coolen LM, Lehman MN, *et al*. Molecular mapping of the neural pathways linking leptin to the neuroendocrine reproductive axis. *Endocrinology* 2011; 152: 2302–10.
- 43 Leshan RL, Pfaff DW. The hypothalamic ventral premammillary nucleus: a key site in leptin's regulation of reproduction. *J Chem Neuroanat* 2014; 61–62: 239–47.
- 44 Sanchez-Garrido MA, Tena-Sempere M. Metabolic control of puberty: roles of leptin and kisspeptins. *Horm Behav* 2013; 64: 187–94.
- 45 True C, Takahashi D, Kirigiti M, Lindsley SR, Moctezuma C, *et al*. Arcuate nucleus neuropeptide coexpression and connections to gonadotrophin-releasing hormone neurones in the female rhesus macaque. *J Neuroendocrinol* 2017; 29: 10.1111/jne.12491.
- 46 Egan OK, Inglis MA, Anderson GM. Leptin signaling in AgRP neurons modulates puberty onset and adult fertility in mice. *J Neurosci* 2017; 37: 3875–86.
- 47 Verma S, Kirigiti MA, Millar RP, Grove KL, Smith MS. Endogenous kisspeptin tone is a critical excitatory component of spontaneous GnRH activity and the GnRH response to NPY and CART. *Neuroendocrinology* 2014; 99: 190–203.
- 48 Tena-Sempere M, Barreiro ML. Leptin in male reproduction: the testis paradigm. *Mol Cell Endocrinol* 2002; 188: 9–13.
- 49 Glander HJ, Lammert A, Paasch U, Glasow A, Kratzsch J. Leptin exists in tubuli seminiferi and in seminal plasma. *Andrologia* 2002; 34: 227–33.
- 50 Hoggard N, Hunter T, Trayhurn P, Williams LM, Mercer JG. Leptin and reproduction. *Proc Nutr Soc* 1998; 57: 421–7.
- 51 Caprio M, Isidori AM, Carta AR, Moretti C, Dufau ML, *et al*. Expression of functional leptin receptors in rodent Leydig cells. *Endocrinology* 1999; 140: 4939–47.
- 52 Tena-Sempere M, Pinilla L, Zhang FP, Gonzalez LC, Huhtaniemi I, *et al*. Developmental and hormonal regulation of leptin receptor (Ob-R) messenger ribonucleic acid expression in rat testis. *Biol Reprod* 2001; 64: 634–43.
- 53 Jensen TK, Andersson AM, Jorgensen M, Andersen AG, Carlsen E, *et al*. Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men. *Fertil Steril* 2004; 82: 863–70.
- 54 Fejes I, Koloszar S, Zavaczki Z, Daru J, Szollosi J, *et al*. Effect of body weight on testosterone/estradiol ratio in oligozoospermic patients. *Arch Androl* 2006; 52: 97–102.
- 55 Hammoud AO, Gibson M, Peterson CM, Meikle AW, Carrell DT. Impact of male obesity on infertility: a critical review of the current literature. *Fertil Steril* 2008; 90: 897–904.
- 56 Hofny ER, Ali ME, Abdel-Hafez HZ, Kamal Eel D, Mohamed EE, *et al*. Semen parameters and hormonal profile in obese fertile and infertile males. *Fertil Steril* 2010; 94: 581–4.
- 57 Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril* 2010; 93: 2222–31.
- 58 Kort HI, Massey JB, Elsner CW, Mitchell-Leef D, Shapiro DB, *et al*. Impact of body mass index values on sperm quantity and quality. *J Androl* 2006; 27: 450–2.
- 59 Isidori AM, Caprio M, Strollo F, Moretti C, Frajese G, *et al*. Leptin and androgens in male obesity: evidence for leptin contribution to reduced androgen levels. *J Clin Endocrinol Metab* 1999; 84: 3673–80.
- 60 Jahan S, Bibi R, Ahmed S, Kafeel S. Leptin levels in infertile males. *J Coll Physicians Surg Pak* 2011; 21: 393–7.
- 61 Leisegang K, Bouic PJ, Menkveld R, Henkel RR. Obesity is associated with increased seminal insulin and leptin alongside reduced fertility parameters in a controlled male cohort. *Reprod Biol Endocrinol* 2014; 12: 34.
- 62 Fernandez CD, Bellentani FF, Fernandes GS, Perobelli JE, Favareto AP, *et al*. Diet-induced obesity in rats leads to a decrease in sperm motility. *Reprod Biol Endocrinol* 2011; 9: 32.
- 63 Fernandez CD, Fernandes GS, Favareto AP, Perobelli JE, Sanabria M, *et al*. Decreased implantation number after *in utero* artificial insemination can reflect an impairment of fertility in adult male rats after exogenous Leptin exposure. *Reprod Sci* 2017; 24: 234–41.
- 64 Li HW, Chiu PC, Cheung MP, Yeung WS, O WS. Effect of leptin on motility, capacitation and acrosome reaction of human spermatozoa. *Int J Androl* 2009; 32: 687–94.
- 65 Haron MN, D'Souza UJ, Jaafar H, Zakaria R, Singh HJ. Exogenous leptin administration decreases sperm count and increases the fraction of abnormal sperm in adult rats. *Fertil Steril* 2010; 93: 322–4.
- 66 Abbasihormozi S, Shahverdi A, Kouhkan A, Cheraghi J, Akhlaghi AA, *et al*. Relationship of leptin administration with production of reactive oxygen species, sperm DNA fragmentation, sperm parameters and hormone profile in the adult rat. *Arch Gynecol Obstet* 2013; 287: 1241–9.
- 67 Almabhouh FA, Osman K, Siti Fatimah I, Sergey G, Gnanou J, *et al*. Effects of leptin on sperm count and morphology in Sprague-Dawley rats and their reversibility following a 6-week recovery period. *Andrologia* 2015; 47: 751–8.
- 68 Almabhouh FA, Osman K, Ibrahim SF, Gupalo S, Gnanou J, *et al*. Melatonin ameliorates the adverse effects of leptin on sperm. *Asian J Androl* 2017; 19: 647–54.
- 69 Caldefie-Chezet F, Poulin A, Sion B, Vasson MP. Leptin: a potential regulator of polymorphonuclear neutrophil bactericidal action? *J Leukoc Biol* 2001; 69: 414–8.
- 70 Fortunato A, Bidegain J, Baltanas A, Moreno MU, Montero L, *et al*. Is leptin involved in phagocytic NADPH oxidase overactivity in obesity? Potential clinical implications. *J Hypertens* 2010; 28: 1944–50.
- 71 Yamagishi S, Amano S, Inagaki Y, Okamoto T, Takeuchi M, *et al*. Pigment epithelium-derived factor inhibits leptin-induced angiogenesis by suppressing vascular endothelial growth factor gene expression through anti-oxidative properties. *Microvasc Res* 2003; 65: 186–90.
- 72 Schroeter MR, Leifheit-Nestler M, Hubert A, Schumann B, Gluckermann R, *et al*. Leptin promotes neointima formation and smooth muscle cell proliferation via NADPH oxidase activation and signalling in caveolin-rich microdomains. *Cardiovasc Res* 2013; 99: 555–65.
- 73 Blanca AJ, Ruiz-Armenta MV, Zambrano S, Salsoso R, Miguel-Carrasco JL, *et al*. Leptin induces oxidative stress through activation of NADPH oxidase in renal tubular cells: antioxidant effect of L-carnitine. *J Cell Biochem* 2016; 117: 2281–8.
- 74 Agarwal A, Saleh RA. Role of oxidants in male infertility: rationale, significance, and treatment. *Urol Clin North Am* 2002; 29: 817–27.
- 75 Aitken RJ, Smith TB, Jobling MS, Baker MA, De Iulius GN. Oxidative stress and male reproductive health. *Asian J Androl* 2014; 16: 31–8.
- 76 de Lamirande E, Gagnon C. Impact of reactive oxygen species on spermatozoa: a balancing act between beneficial and detrimental effects. *Hum Reprod* 1995; 10 Suppl 1: 15–21.
- 77 Shiraishi K, Naito K. Effects of 4-hydroxy-2-nonenal, a marker of oxidative stress, on spermatogenesis and expression of p53 protein in male infertility. *J Urol* 2007; 178: 1012–7.
- 78 Agarwal A, Ikemoto I, Loughlin KR. Relationship of sperm parameters with levels of reactive oxygen species in semen specimens. *J Urol* 1994; 152: 107–10.
- 79 Kemal Duru N, Morshedi M, Dehninger S. Effects of hydrogen peroxide on DNA and plasma membrane integrity of human spermatozoa. *Fertil Steril* 2000; 74: 1200–7.
- 80 Aziz N, Saleh RA, Sharma RK, Lewis-Jones I, Esfandiari N, *et al*. Novel association between sperm reactive oxygen species production, sperm morphological defects, and the sperm deformity index. *Fertil Steril* 2004; 81: 349–54.
- 81 Mahfouz RZ, du Plessis SS, Aziz N, Sharma R, Sabanegh E, *et al*. Sperm viability, apoptosis, and intracellular reactive oxygen species levels in human spermatozoa before and after induction of oxidative stress. *Fertil Steril* 2010; 93: 814–21.
- 82 Agarwal A, Prabakaran SA, Said TM. Prevention of oxidative stress injury to sperm. *J Androl* 2005; 26: 654–60.
- 83 Angelopoulou R, Kyriazoglou M. Sperm oxidative damage and the role of reactive oxygen species in male infertility. *Arch Hellen Med* 2005; 22: 433–46.
- 84 Weir CP, Robaire B. Spermatozoa have decreased antioxidant enzymatic capacity and increased reactive oxygen species production during aging in the Brown Norway rat. *J Androl* 2007; 28: 229–40.
- 85 Md Mokhtar AH, Malik IA, Abd Aziz NAA, Almabhouh FA, Durairajanayagam D, *et al*. LY294002, a PI3K pathway inhibitor, prevents leptin induced adverse effects on sperm in Sprague-Dawley rats. *Andrologia* 2018. doi: 10.1111/and.13196. [Epub ahead of print].
- 86 Ibrahim HS, Froemming GR, Omar E, Singh HJ. ACE2 activation by xanthone prevents leptin-induced increases in blood pressure and proteinuria during pregnancy in Sprague-Dawley rats. *Reprod Toxicol* 2014; 49: 155–61.
- 87 Farhana K, Effendi I, Caszo B, Satar NA, Singh HJ. Exercise prevents leptin-induced increase in blood pressure in Sprague-Dawley rats. *J Physiol Biochem* 2014; 70: 417–23.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.