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Role of AMPK in mammals reproduction: Specific controls and whole-body energy sensing

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ABSTRACT

AMP-activated protein kinase (AMPK) is a key enzyme involved in linking the energy sensing to metabolic pathways. As such, it plays a central role at the whole-body level to translate endocrine communications into adapted responses aimed either at saving energy when food is scarce or at allocating it to various functions, particularly reproduction, when food is available. AMPK also plays major roles in the energy individual cells use in order to realize their specific functions. This is of course especially true for all cells involved in the reproductive function (gonads, gametes) or in its control (hypothalamus, pituitary). In the present review, I report a survey of the various roles of AMPK functions in reproduction, either directly in reproductive organs, or indirectly in organs controlling reproduction, particularly at hypothalamus level.

1. Introduction

Reproduction is an energy-consuming function and is therefore either restricted or inhibited in cases of limited available energy status in animals. As a sensor of cellular energy status, AMP-activated protein kinase (AMPK) plays a central role in maintaining energy homeostasis intracellularly as well as in whole-body energy metabolism. It is thus involved in reproduction control through its indirect and general energy sensing role, but also through its direct specific action on cellular functions at different levels of reproduction control (hypothalamus, pituitary, ovaries, testes) as well as in gametes (oocytes and spermatozoa) or on fertilization and early embryo development.

AMPK responds to changes in intracellular adenine nucleotide levels, as it is activated by an increase in AMP/ADP relative to ATP. Activation of AMPK increases the rate of catabolic (ATP-generating) pathways and decreases the rate of anabolic (ATP-utilising) pathways.

In the present review, I will essentially consider the direct effects of AMPK at the central and peripheral levels of reproduction control in mammals, but also its indirect roles on reproduction through endocrine or neuro-endocrine controls of whole-body energy homeostasis.

2. AMPK structure

AMPK is a serine/threonine heterotrimeric kinase consisting of a catalytic α-subunit and regulatory β- and γ-subunits. Further complexity is added by the existence of multiple subunits genes encoding each isoform of each subunit. In mammals, there are two genes encoding the AMPK α catalytic subunit (α1 and α2), two β genes (β1 and β2), and three γ subunit genes (γ1, γ2, and γ3) [1]. AMPK is activated by the phosphorylation of a threonine residue (Thr-172) at a catalytic α subunit within the activation loop of the kinase domain by upstream kinases, including STK11: serine/threonine kinase

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11 [LKB1] [2,3], calmodulin-dependent kinase kinase-β [CaMKKβ] [4], or TGF-β-activated kinase-1 [TAK1] [5,6], and regulating the dephosphorylation of Thr172 via phosphatases (phosphatase-2 [PP2A or PP2C]) [7].

In addition to the phosphorylation of Thr172 by AMPK kinases, AMPK can be activated, more or less directly, by several pharmacological agents. Metformin and other biguanides, like phenformin [8], indirectly activate AMPK by inhibiting Complex 1 of the respiratory chain, which, in turn, decreases intracellular ATP levels [9]. Structurally similar to adenosine, the AMPK agonist 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) is converted by adenosine kinase to the monophosphorylated nucleotide ZMP. ZMP binds to cystathionine-beta-synthase (CBS) domains of the AMPK γ subunit, allowing allosteric activation and increased phosphorylation of Thr172 [10]. Moreover, some natural compounds, like resveratrol, which is found, for instance, in the skin of red grapes [11,12], activate AMPK and have a beneficial effect on metabolic diseases comparable to those of AICAR and metformin. This compound acts in a quick fashion by inhibiting the F1F0 mitochondrial ATPase [9] and seems to activate Sirtuins 1 (SIRT1) through increased NAD^+ levels, induced themselves by AMPK activity [13,14].

Unlike AICAR and metformin, A769662 does not increase cellular ADP/ATP or AMP/ATP ratios [15], and is therefore considered to directly activate AMPK in cells, expressing an AMP-insensitive mutant [9]. Accordingly, it stimulates AMP-insensitive AMPK mutants. Moreover, it does not displace AMP from its binding sites on the γ subunit, suggesting that it binds at a different site, even though, like AMP, it causes both allosteric activation and protection against Thr172 dephosphorylation [16,17]. A769662 is also selective for the activation of β1 rather than that of β2 complexes, and its effects are abolished by an S108 mutation in β1 that prevents the autophosphorylation of that serine residue, suggesting that the binding site involves the β subunit [15,17]. The activity of AMPK is inhibited by (6-[4-(2-piperidin-1-yl-ethoxy)-phenyl)]3-pyridin-4-yl-pyrazolo[1,5-a] pyrimidine [18], known as compound C or dorsomorphin. It can also block the uptake of AICAR into cells and thus inhibit AICAR stimulatory effects [19]. In addition, when incubated with either AICAR or metformin, compound C hinders the inactivation of acetyl CoA carboxylase (ACC) [20].

3. Reproduction control at the central level

AMPK is expressed in the hypothalamus and is able to integrate nutritional and hormonal signals to adapt feeding behaviour and energy expenditure [21]. The hypothalamo-hypophyseal complex controls central reproductive function, allowing the secretion of "gonadotropin-releasing hormone" (GnRH) by the hypothalamus as well as gonadotropins: "luteinizing hormone" (LH) and "follicle-stimulating hormone" (FSH) by the pituitary.

There are many factors affecting energy intake and energy expenditure via the activation (ghrelin, adiponectin, glucocorticoids, cannabinoids) or inhibition (oestradiol, leptin, insulin, GPL-1) of AMPK at the hypothalamus level [22]. At the central level, hypothalamic activated AMPK restores energy balance by promoting feeding behaviour to increase energy intake, increasing glucose production, and reducing energy output. Glucose deprivation causes a decrease in the secretion of hypothalamic hormones, and AMPK is implicated in the sensitivity to glucose variations of GnRH neurons in rats [23,24].

AICAR increased phosphorylations of AMPK and ACC specifically in the hypothalamus, significantly increasing food intake and significantly decreasing the period between two oestrous cycles in the rat [25]. AICAR and adiponectin also inhibited GnRH secretion from GT1-7 hypothalamic GnRH neuron cells through AMPK activation and inhibition of extracellular signal-regulated kinase (ERK) [26]. Adiponectin also inhibited KISS1 gene transcription, which is the upstream signal of GnRH [27,28]. On cell cultures of hypothalamic neurons from rat foetuses (E18 and E19 [29]), treatment with metformin coupled with low glucose concentrations reduced the phosphorylation of AMPK. This decrease in phosphorylation allowed the increase of neuropeptide Y (NPY) expression [30]. NPY participates in the regulation of reproductive functions primarily by modulating GnRH and gonadothropins (LH, FSH) in the central nervous system of several species [31,32]. Metformin activation of AMPK also inhibited FSH and LH secretions by inhibiting two proteins responsible for their secretion: "Mitogen-activated protein kinase" (MAPK) 3/1 and SMAD2 in rat pituitary cell cultures [33]. The MAPK/ERK pathway plays an important role in the regulation of gene expression, especially in proliferation, differentiation, and apoptosis processes [34]. On the one hand, ERK has been characterized as being negatively regulated by AMPK [35] and, on the other hand, as an element regulating the secretion of GnRH [36], making it a possible candidate for the inhibition of GnRH secretion by AMPK at the central level.

Moreover, adipose tissue-derived signalling molecules play a major role in whole-body energy homeostasis. Responding to nutrient flux, it secretes hormones such as adiponectin and leptin, as well as fatty acids [37]. Pharmacological inhibition of AMPK abolished the increase in adiponectin-stimulated glucose uptake by adipocytes, demonstrating that AMPK is involved in autocrine action of adiponectin at the adipocyte level [38]. Adiponectin decreases hepatic lipogenesis and increases β-oxidation also through the adipoR1-mediated activation of AMPK and the peroxisome proliferator-activated receptor (PPARα). The communication between adipose tissue and liver is crucial to the maintenance of systemic, whole-body, energy homeostasis, and adiponectin has thus been shown to be involved in both organs through AMPK activation. Leptin increases skeletal muscle fatty acid oxidation and decreases triglyceride accumulation via the activation of AMPK [39]. Moreover, AMPK activation limits the effects of high-fat-diet-induced renal dysfunction [40]. All these examples show that AMPK plays pleiotropic roles in whole-body energy balance, with an indirect effect on reproduction, which is favoured when this balance is positive.

4. AMPK at the level of ovary

The presence of AMPK has been identified in different ovarian cells: oocytes, granulosa cells, theca cells, corpus luteum, cumulus cells, in several vertebrate species [41–45]. AMPK plays a role in the steroidogenesis of granulosa cells. After pharmacological stimulation with AICAR or metformin, AMPK inhibits the secretion of two steroid hormones: oestradiol and progesterone [41,43–45]. These decreases are explained by the inhibition of the expression of steroidogenic acute regulatory (StAR) protein [44] and two key enzymes of steroidogenesis: 3β-hydroxysteroid-dehydrogenase (3β-HSD) [41], p450 side chain cleavage (p450scc) [44]. Inhibition of oestradiol and progesterone has also been characterized as passing through the inhibition of the MAPK/ERK pathway [41,44]. In addition, the activation of AMPK allows the blocking of GVBD in oocytes surrounded by cumulus of cow and sow cells [46–48], whereas in mice, the activation of AMPK triggers GVBD in both oocytes and oocytes surrounded by cumulus cells [49]. On the same key and particularly conserved mechanism, the effects of AMPK may vary depending on the species, requiring a better understanding of the specific mechanisms of each species, especially the cessation of meiosis before GVBD [50].

Metabolic hormones such as leptin, resistin, adiponectin (three adipokines), and ghrelin, seem to act, at least in part, through AMPK signalling [22]. Therefore, systemic energy homeostasis also exerts an indirect control on ovarian function. Energy balance defects, and thereby metabolic abnormalities, can lead to the development of some physiopathological conditions such as polycystic ovary syndrome (PCOS). Indeed, women with PCOS exhibit altered fertility mostly associated with metabolic disorders such as insulin resistance, hyperinsulinemia, and/or dyslipidaemia. Metformin, an insulin-sensitizer and also indirect AMPK activator, is used for the treatment of women with PCOS and restores subnormal fertility together with recovered energy balance.

5. AMPK at the level of testis

LKB1 and AMPK kinases have been identified in rat testes, specifically in germ cells, Leydig cells and Sertoli cells [51]. Several AMPK-related kinases: MARK4, BRSKs, NUARk2, and SNRK have also been characterized in the testis [52–54].

The final number of Sertoli cells reached during the proliferative period determines the level of sperm production in adults. FSH gonadotropin, a major mitogen of Sertoli cells, has been characterized as an inhibitor of AMPK. In addition, pharmacological activation of AMPK provides inhibition of Sertoli cell proliferation via the inhibition of mTORC [55]. By decreasing the number of Sertoli cells, activated AMPK would therefore decrease the amount of spermatozoa produced. Inactivation of AMPK α1 in somatic and germinal rat testes cells has shown the role of AMPK in sperm quality [56]. Tartarin et al. raised in 2012 the idea that AMPK would be involved in the establishment of the cytoskeleton in Sertoli cells and germ cells, particularly in the organization of mitochondria and the design of the shape of the spermatozoa head. Specific deletion of the AMPKα1 gene in the Sertoli cells in mice (Sc-AMPKα1KO mice) has led to a 25% reduction in male fertility, associated with abnormal spermatozoa with a thin head and dysregulated energy metabolism with altered lactate, lipid, and ATP production [57]. These results are supported by the observation of the involvement of AMPK in maintaining a dense junctional cellular tissue between Sertoli cells, thus contributing to the preservation of an optimal environment for quality spermatogenesis [58]. AMPK and LKB1 would also be involved in reproductive success by influencing motility [59,60]. In the testes where AMPK was knocked out, the poor organization of mitochondria in spermatozoa coupled with their decreased motility would be explained by the involvement of AMPK in mitochondrial biogenesis [61]. At the level of the testicle, activated AMPK would have a contrasting effect on spermatozoa, on the one hand decreasing the amount of spermatozoa produced by inhibiting the proliferation of Sertoli cells and, on the other hand, ensuring the quality of spermatozoa via mobility and the structure of the head, optimizing the organization of somatic cells. AMPK is also involved in testicular steroidogenesis. In fact, in the testes where AMPK was inhibited, there are a 5-fold increase in cholesterol and a significant increase in the protein level of a cholesterol carrier (StAR) and two enzymes involved in steroid production (P450c17 and 3βHSD); this disturbance could affect spermatogenesis [56].

In primary rat Leydig cells, resveratrol, an AMPK agonist, impairs human chorionic gonadotropin (hCG)-mediated testosterone production by repressing StAR expression [62]. In humans, the association of increased steroid production with inhibition of AMPK could be associated with the familial hamartoma syndrome, Peutz–Jeghers Syndrome (PJS) [63,64]. Loss of function mutations in STK11, encoding the Ser/Thr protein kinase, LKB1, are responsible for PJS. LKB1 phosphorylates and activates AMPK in response to energy stress and thus plays a key role in energy homeostasis. The hypothesis guiding this proposal is that the LKB1-AMPK signalling axis evolved to limit cell growth under conditions of energy stress and that genetic or epigenetic aberrations, as well as transcriptional and post-transcriptional events that suppress LKB1 function, allow tumour cells to override metabolic control mechanisms that normally limit cell growth under energy stress [65].

6. AMPK at the level of spermatozoa

Recent discoveries show that AMPK is present in several parts of spermatozoa from different species such as in the acrosome, the head's sub-equatorial segment, the intermediate piece, the midpiece, and the flagellum. It has been demonstrated that it plays relevant roles in spermatozoa by regulating motility as well as plasma membrane fluidity and organization and acrosome integrity, whereas it contributes to the maintenance of the mitochondrial membrane potential [51]. The role of AMPK has been studied in detail in spermatozoa by using pharmacological agents acting as AMPK modulators (Table 1).

Table 1
List of pharmacological agents commonly used to activate AMPK in intact sperm cells and their mechanisms of action.

Agent	Mechanism
Metformin, AICAR	Chicken [66,72]: increase sperm motility, viability, acrosome reaction, ATP, and lactate production in fresh sperm; improve post-thaw motility and AR of healthy sperm by restoring ATP level and antioxidant system (SOD, GPx, GR), and reduce oxidative stress and lipid peroxidation Mouse [73]: no effect on viability and acrosome membrane integrity in fresh sperm. Decrease sperm motility and active mitochondria in fresh sperm; increase frozen-thawed sperm viability, membrane integrity, and fertilized oocytes rate Stallion [77]: no effect on: viability and motility after cryopreservation
A-769662	Boar [78]: decreases sperm motility, rapid sperm rate and other motility parameters (VCL, VSL, VAP). Prevents the decline in cell viability; increases lipid disorganization and phosphatidylserine externalization in sperm plasma membrane, and diminishes acrosome membrane integrity Human [79]: increases the percentage of motile, progressive, and rapid sperm; no effect on sperm viability; no effect on mitochondrial membrane potential or reactive oxygen species production, acrosome membrane integrity, phosphatidylserine exposure at plasma membrane
Resveratrol	Human [69–71]: decreases DNA integrity in frozen-thawed sperm; increases mitochondrial membrane potential and decreases reactive oxygen species and apoptosis-like changes in frozen-thawed spermatozoa; no effect on motility parameters, except a significant reduction in motility in fresh and frozen-thawed spermatozoa
Compound C	Chicken [66,72]: decreases sperm motility, viability acrosome reaction, ATP, and lactate production in fresh and frozen-thawed sperm; decreases ATP level and antioxidant system (SOD, GPx, GR), and increases the oxidative stress and lipid peroxidation Boar [59,80]: decreases the percentage of motile and rapid sperm and other motility parameters (VAP, VCL, VSL, LIN, STR, WOB, ALH, and BCF); decreases the mitochondrial membrane potential, plasma membrane lipid organization, outward phosphatidylserine exposure, acrosome integrity Human [67,68,77]: decreases the percentage of motile sperm, sperm velocity, progressivity, and VCL, VSL, VAP, ALH, LIN, BCF; increases DNA integrity in frozen-thawed human sperm; decreases the percentage of reactive oxygen species, apoptosis-like changes, mitochondrial membrane potential, and motility parameters

The presence of AMPK in the acrosome suggests that it plays a role in the agonist-induced acrosome reaction [66]. In addition, the localization of phospho-AMPK in the spermatozoa flagellum of several species suggests that it acts through the phosphorylation of protein substrates involved in the functioning of the axoneme (a central apparatus that is essential for flagellar motility). The mechanism could be similar to that demonstrated for a testicular AMPK-related kinase: Testis-Specific Serine Kinase 2 (TSSK2), a Ser/Thr protein kinase close to AMPK [67]. TSKK2 phosphorylates SPAG16L, a protein of the axoneme central apparatus, which is essential for mouse spermatozoa flagellar motility [68]. These results are in agreement with the fact that ATP production is not limited to the spermatozoa intermediate piece (mitochondrial respiration), but may also occur at other places via anaerobic glycolysis [15,18].

The key role of AMPK in the control of cell energy homeostasis has made it an important kinase regarding the regulation of spermatozoa functions. Indeed, these functions, such as motility, acrosome reaction, and fertilization, are very dependent on energy levels. It has also been recently shown that AMPK helps restoring spermatozoa functions after cryopreservation [69–73] by increasing the activity of antioxidant enzymes and reducing the production of ROS and LPO [72]. The positive effects of AMPK stimulation on spermatozoa functions after cryopreservation supports the hypothesis of its "protector" role on gametes after exposure to extreme cold and osmotic stress conditions encountered during the freeze/thaw process.

Specific deletion of the AMPKα1 gene in the Sertoli cells in mice (Sc-AMPKα1KO mice) has led to a 25% reduction in male fertility, associated with abnormal spermatozoa with a thin head and dysregulated energy metabolism with altered lactate, lipid, and ATP production [51,57]. It is therefore expected that regulators (FSH, insulin, testosterone) of Sertoli cell functions, among them AMPK activity, will influence spermatogenesis. In rat Leydig cells, the use of the AMPK activator resveratrol decreased testosterone secretion through a reduction in cholesterol transport into the mitochondria and decreased conversion of progesterone into androstenedione [62].

7. Conclusion

All energy-requiring reactions in the cell use energy from ATP hydrolysis, so it is no surprise that AMPK, which is involved in cellular energy balance, plays a central role in reproduction, which requires a sufficient energetic status. In this review, important roles of AMPK have been reported in the development of female and male gonads, gamete production as well as in hypothalamus through hormonal control. AMPK is the target of an increasing number of pharmacological modulators that could be useful in the control of reproduction or for correcting infertility problems.

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