Hypothesis

A Hypothetical Role for Geranylgeranoic Acid as a Lipid Mediator in Male Reproductive Physiology

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A Hypothetical Role for Geranylgeranoic Acid as a Lipid Mediator in Male Reproductive Physiology

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Abstract

Geranylgeranoic acid (GGA) is a naturally occurring C_{20} isoprenoid lipid that has garnered attention for its anticancer and retinoid-like properties. While its hepatic functions are well documented, its role in male reproductive physiology remains unexplored. Emerging evidence—including the detection of GGA in testis, epididymis, prostate, and even human seminal fluid—suggests a physiological presence in the male reproductive tract. Furthermore, dietary GGA supplementation in mice has been linked to increased offspring survival. These findings prompt the hypothesis that GGA acts as a lipid-derived modulator of male fertility, influencing sperm maturation, local signaling, or fertilization capacity. Here, we explore this hypothesis through the lens of GGA's biosynthesis, tissue distribution, receptor interactions, and possible eicosanoid-like signaling roles. We propose experimental strategies, ranging from lipidomic profiling to receptor screening and functional assays, to validate the physiological and reproductive relevance of this underrecognized metabolite.

Keywords: geranylgeranoic acid; lipid mediator; male reproductive system; isoprenoid metabolism; fertility regulation

Chapter 1: Introduction

Mammalian reproductive success depends on a complex network of molecular signals that govern gametogenesis, hormonal communication, and cellular interactions within reproductive tissues. While steroid hormones and prostaglandins have long been recognized as key modulators of male fertility[1,2], recent advances in lipidomics suggest that other, lesser-known isoprenoid-derived lipids may also contribute to the regulation of reproductive processes[3]. Among these, geranylgeranoic acid (GGA), a C_{20} polyunsaturated fatty acid synthesized via the mevalonate pathway[4], has garnered attention for its diverse biological activities, including pyroptosis induction[5,6], and suppression of hepatic tumorigenesis[7,8].

GGA and its 4,5-didehydro derivative were initially investigated as synthetic analogs of retinoic acid[9], capable of promoting cellular differentiation without inducing significant toxicity[10,11]. Subsequently, it was identified as a naturally occurring metabolite in both plants[12,13] and mammalian tissues[4,8], with particularly high concentrations in the liver[4]. Recent studies have elucidated its endogenous biosynthesis, which involves hepatic enzymes such as monoamine oxidase B (MAOB)[14] and cytochrome P450 3A4 (CYP3A4)[15], which are highly expressed in hepatic cells[16–19]. Despite these advances, the full spectrum of GGA's biological functions remains largely unexplored[16,17].

Intriguingly, preliminary analyses have detected the presence of GGA in the male reproductive organs of laboratory rats (Sprague–Dawley and Wistar strains) and mice (C3H/HeN and C57BL/6 strains), including the testis, epididymis, and prostate *(Tabata* et al., *unpublished data)*. Moreover, trace levels of GGA have been identified in human seminal fluid, although these findings have not yet been published *(Tabata* et al., *unpublished data)*. These observations raise the possibility that GGA

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may exert physiological functions in the male reproductive system, potentially influencing sperm maturation, capacitation, or fertilization.

Another compelling observation arises from animal studies, where dietary GGA supplementation resulted in a significant increase in the number of weaned offspring, suggesting either enhanced fertilization efficiency or improved neonatal survival[20,21]. Although the underlying mechanism remains unclear, this phenotype merits further investigation. Structurally, GGA is an isomer of arachidonic acid[4], a key precursor of prostaglandins, which are well-known for their role in regulating reproductive functions, including sperm motility and fertilization[1,22]. This structural relationship, combined with its localization in male reproductive tissues, raises an intriguing question: Could GGA represent a novel class of prostaglandin-like modulators involved in male reproduction?

In this hypothesis article, we propose that GGA functions as a non-classical lipid mediator in the male reproductive tract. We present supporting preliminary data, draw conceptual parallels with established lipid signaling molecules, and propose future experimental approaches to test this hypothesis. Elucidating the role of GGA in reproductive physiology may yield novel insights into the regulation of male fertility and offer new avenues for nutritionally or pharmacologically enhancing reproductive health.

Chapter 2: Localization of GGA in Male Reproductive Organs

Geranylgeranoic acid (GGA) has traditionally been studied in the context of hepatic metabolism and cancer prevention[13,23–30]. However, accumulating evidence suggests that GGA is not confined to hepatic tissues but is also present in male reproductive organs. In our previous study, we detected measurable levels of GGA in the testis, epididymis, and prostate of adult Wistar rats, indicating that its physiological functions may extend beyond hepatic homeostasis[4]. These findings open new avenues for investigating the function of GGA in reproductive biology.

Moreover, unpublished preliminary data indicate the presence of GGA in male reproductive organs in two strains of mice, C3H/HeN and C57BL/6. Although these data have not yet been peer-reviewed, the reproducibility across species and strains suggests a conserved distribution pattern of GGA within male-specific tissues. Notably, these organs are known sites of lipid signaling and hormone production, positioning them as plausible targets for isoprenoid-related modulation studies[1,2].

The detection of GGA in human semen (n=1, unpublished) broadens the potential physiological relevance of this metabolite. Although the data are preliminary and derived from a self-sampling protocol not reviewed by an institutional ethics committee, they suggest that GGA may be secreted or excreted into the seminal fluid. This raises intriguing possibilities regarding its potential role in sperm maturation, motility, and intercellular communication during fertilization. Together, these observations warrant deeper investigation into the distribution and metabolism of GGA within the male reproductive system. The expression of key enzymes involved in GGA biosynthesis and metabolism, such as monoamine oxidase B (MAOB) and Cyp3a11, the murine homolog of human CYP3A4, in testicular and prostatic tissues supports the possibility of local synthesis or metabolic transformation[18,19,31,32]. Future studies should aim to validate these findings using larger sample sizes, ethically approved sampling protocols, and high-resolution techniques such as spatial transcriptomics or immunohistochemistry to precisely map the localization of these enzymes.

Furthermore, the potential crosstalk between GGA signaling and neurotrophic pathways, including brain-derived neurotrophic factor (BDNF)[33–35] and its receptor, the tropomyosin receptor kinase B (TrkB)[34], represents a promising avenue for mechanistic investigation. Given the emerging roles of BDNF–TrkB signaling in sperm maturation and motility, it is conceivable that GGA may intersect with these pathways to modulate male reproductive function at the molecular level.

Chapter 3: Hypothetical Roles of GGA in Male Fertility and Reproduction

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The physiological presence of geranylgeranoic acid (GGA) in the male reproductive organs invites speculation regarding its potential biological role in fertility and reproductive function. Although no direct evidence links GGA to spermatogenesis or male reproductive success, several converging lines of reasoning suggest plausible mechanisms by which GGA may influence these processes.

3.1. A Retinoid-Like Modulator in Male Tissues

GGA was initially synthesized as a retinoid-like compound that capable of induce differentiation and apoptosis in hepatoma cells[9,36,37]. Retinoic acid and its derivatives are well-known for their roles in male germ cell development, particularly in the regulation of spermatogonial differentiation[38,39]. Given its structural resemblance and functional overlap with retinoids, GGA may exert comparable effects in the testis and epididymis. For example, GGA can act through nuclear receptors or other lipid-sensitive transcriptional regulators to modulate gene expression in germ cells or Sertoli cells.

Recent studies have highlighted the involvement of brain-derived neurotrophic factor (BDNF) and its receptor TrkB in the regulation of spermatogenesis, particularly in the modulation of Sertoli cell function and germ cell survival[33,35]. Given the retinoid-like properties of GGA and its potential nuclear signaling activity, it is conceivable that GGA may interact with or modulate the BDNF–TrkB axis in male reproductive tissues. Further investigations are warranted to determine whether GGA can influence neurotrophin signaling as part of its reproductive regulatory role.

3.2. A Putative Seminal Signaling Molecule

The detection of GGA in human semen, though still preliminary, suggests that GGA may serve as a signaling molecule during fertilization(Tabata et al., unpublished data). A useful analogy can be drawn with prostaglandins, which are derived from arachidonic acid (C_{20}:4) and play essential roles in seminal plasma function, sperm motility, and uterine interactions[22,40]. Structurally, GGA is a C_{20} isoprenoid with four double bonds, making it a structural isomer of arachidonic acid. This raises the hypothesis that GGA could act as a "second generation" lipid mediator, potentially modulating immune tolerance, oxidative balance, or sperm–egg recognition within the female reproductive tract.

3.3. Impact on Offspring Viability

Our previous data suggest that dietary supplementation with GGA increases the number of pups surviving to weaning, potentially through enhanced paternal contributions[20,21]. This observation raises the hypothesis that GGA may support sperm quality, genomic integrity, or epigenetic programming, thereby influencing embryonic development and offspring fitness. Although the underlying mechanisms remain unclear, possible pathways include antioxidant activity, mitochondrial modulation, or nuclear receptor-mediated signaling, each of which warrants targeted investigation.

3.4. Biosynthetic Capacity in Reproductive Tissues

Expression analyses suggest that MAOB and cyp3a11, enzymes involved in the oxidative conversion of geranylgeraniol (GGOH) to GGA, are expressed in male reproductive tissues, such as the testis and prostate[18,19,31,32]. Supporting this, previous studies have demonstrated that the GGOH-derived metabolite geranylgeranyl pyrophosphate (GGPP) plays a functional role in prostate cells[41] by modulating androgen receptor signaling, a process that can be rescued by exogenous GGOH supplementation in GGPP-depleted conditions. This supports the idea that GGA is synthesized locally within the reproductive tract rather than being imported from hepatic sources. Such tissue-specific production implies localized biological activity, possibly potentially regulated by hormonal cycles or to oxidative stress.

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Chapter 4: Future Directions and Experimental Strategies

The proposed hypothesis that geranylgeranoic acid (GGA) may function as a novel lipid mediator within the male reproductive system opens several promising avenues for research. Although current data remain limited and largely preliminary, the following strategies may serve to validate, refine, or refute of this conceptual framework:

4.1. Quantitative Profiling Across Tissues and Species

To establish the physiological relevance of GGA in reproduction, systematic quantification of GGA across male reproductive tissues in multiple species is warranted. Existing data from Wistar rats, C3H/HeN mice, and B6 mice suggest reproducible detection in the testis, epididymis, and prostate. Expanding this survey to include additional mouse strains, non-rodent mammals, and different developmental stages could help define the distribution and regulation of GGA in the reproductive axis. Techniques such as LC-MS/MS coupled with isotopic standards should be employed to ensure accurate and reproducible measurements.

4.2. Cellular Localization and Enzyme Expression

Understanding which cell types produce or respond to GGA is critical for elucidating its physiological role in the male reproductive system. Immunohistochemical or in situ hybridization analyses of MAOB and CYP3A4 (cyp3a11 in mice) in testicular tissue[32] could help identify the cellular sites of GGA biosynthesis. Simultaneous visualization of GGA itself–if achievable through chemical derivatization or lipid imaging techniques–would help distinguish between intracellular and extracellular localization. Comparative expression profiling of these enzymes in Sertoli cells, Leydig cells, and germ cells across developmental stages and under varying hormonal conditions would provide insights into the regulatory dynamics of GGA metabolism. In addition to nuclear receptor pathways, recent studies have highlighted the role of neurotrophins such as brain-derived neurotrophic factor (BDNF) and its receptor TrkB in male reproductive physiology, particularly in the regulation of Sertoli cell function and germ cell survival[33–35]. Given GGA's retinoid-like signaling capacity, future studies should also assess whether GGA modulates BDNF–TrkB signaling in testicular tissues. This could involve transcriptomic analysis, TrkB phosphorylation assays, or the use of BDNF/TrkB inhibitors in organotypic cultures.

4.3. Functional Assays Using GGA Supplementation or Inhibition

To elucidate the functional role of GGA in male fertility, animal studies involving dietary GGA supplementation during the mating period could assess endpoints such as sperm count, motility, fertilization success, and pup viability. Conversely, pharmacological inhibition of MAOB or CYP enzymes (e.g., via clorgyline or ketoconazole) may be employed to examine whether depletion of endogenous GGA impairs fertility. Ketoconazole, a broad-spectrum antifungal agent, has been shown to affect male reproductive function in both preclinical and clinical settings. In male rats, high-dose ketoconazole transiently reduced serum testosterone and sperm motility without significantly impacting fertility. In mice, it led to approximately a 50% decrease in fertility, accompanied by reductions in seminal protein content[42]. Human observational data also suggest associations between ketoconazole exposure and decreased sperm motility and testosterone levels, while a clinical case in a dog reported reversible azoospermia following prolonged ketoconazole therapy[42–44]. In vitro approaches—including germ cell lines, primary Sertoli cell cultures, and organotypic testis cultures—could be employed to dissect the mechanistic actions of GGA at the cellular level, such as its influence on differentiation, survival, or hormone responsiveness.

4.4. Exploration of Downstream Metabolites and Receptor Targets

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As a C_{20} polyunsaturated fatty acid, GGA may be enzymatically converted into bioactive lipid mediators, possibly acting in an eicosanoid-like manner. Lipidomic analyses of seminal plasma or male reproductive tissues following GGA administration could help identify such downstream metabolites. In parallel, nuclear receptor screening—targeting candidates such as retinoid X receptor (RXR), peroxisome proliferator-activated receptors (PPARs), and retinoic acid receptor-related orphan receptors (RORs)—along with transcriptomic profiling, may uncover signaling pathways modulated by GGA at the transcriptional level.

4.5. Ethical and Clinical Considerations

Although human data remain scarce, the preliminary detection of GGA in semen (n = 1) highlights the need for ethical research frameworks that facilitate small-scale, anonymized studies involving human bodily fluids. Longitudinal studies in healthy volunteers or men experiencing subfertility could help determine whether seminal GGA levels correlate with sperm quality, reproductive outcomes, or overall fertility status. Such investigations would require approval from institutional review boards (IRBs) and the implementation of transparent data-sharing protocols to ensure ethical compliance and reproducibility.

Chapter 5. Conclusion

Geranylgeranoic acid (GGA), a bioactive diterpenoid primarily studied for its hepatic functions, may also play a previously underappreciated role in male reproductive physiology. Based on preliminary biochemical findings and structural parallels with retinoic acid and arachidonic acid, we propose that GGA functions as a local lipid mediator within the male reproductive tract. Its presence in reproductive organs and seminal fluid suggests a broader physiological footprint that could influence sperm development, intercellular signaling, and offspring viability. Future investigations integrating lipidomics, functional assays, and cross-species analyses will be essential to test this hypothesis and to elucidate novel connections between isoprenoid metabolism and reproductive health.

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References

1. Hoxha, M.; Barbonetti, A.; Zappacosta, B. Arachidonic Acid Pathways and Male Fertility: A Systematic Review. *Int. J. Mol. Sci.* **2023**, *24*, 8207, doi:10.3390/ijms24098207.
2. Li, L.; Lin, W.; Wang, Z.; Huang, R.; Xia, H.; Li, Z.; Deng, J.; Ye, T.; Huang, Y.; Yang, Y. Hormone Regulation in Testicular Development and Function. *Int. J. Mol. Sci.* **2024**, *25*, 5805, doi:10.3390/ijms25115805.
3. Zhang, J.-L.; Lv, M.; Yang, C.-F.; Zhu, Y.-X.; Li, C.-J. Mevalonate Pathway and Male Reproductive Aging. *Mol. Reprod. Dev.* **2023**, *90*, 774–781, doi:10.1002/mrd.23705.
4. Shidoji, Y.; Tabata, Y. Unequivocal Evidence for Endogenous Geranylgeranoic Acid Biosynthesized from Mevalonate in Mammalian Cells. *J. Lipid Res.* **2019**, *60*, 579–593, doi:10.1194/jlr.M090548.
5. Yabuta, S.; Shidoji, Y. TLR4-Mediated Pyroptosis in Human Hepatoma-Derived HuH-7 Cells Induced by a Branched-Chain Polyunsaturated Fatty Acid, Geranylgeranoic Acid. *Biosci. Rep.* **2020**, *40*, BSR20194118, doi:10.1042/BSR20194118.
6. Shidoji, Y. Induction of Hepatoma Cell Pyroptosis by Endogenous Lipid Geranylgeranoic Acid-A Comparison with Palmitic Acid and Retinoic Acid. *Cells* **2024**, *13*, 809, doi:10.3390/cells13100809.
7. Shidoji, Y. Geranylgeranoic Acid, a Bioactive and Endogenous Fatty Acid in Mammals: A Review. *J. Lipid Res.* **2023**, *64*, 100396, doi:10.1016/J.JLR.2023.100396.

 doi:10.20944/preprints202506.2134.v3

8. Tabata, Y.; Omori, M.; Shidoji, Y. Age-Dependent Decrease in Hepatic Geranylgeranoic Acid Content in C3H/HeN Mice and Its Oral Supplementation Prevents Spontaneous Hepatoma. *Metabolites* **2021**, *11*, 634, doi:10.3390/metabo11090634.
9. Araki, Hiroshi; Shidoji, Yoshihiro; Yamada, Yasuhiro; Moriwaki, Hisataka; Muto, Y. Retinoid Agonist Activities of Synthetic Geranyl Geranoic Acid Derivatives. *Biochem. Biophys. Res. Commun.* **1995**, *209*, 66–72, doi:10.1006/bbrc.1995.1471.
10. Muto, Y.; Moriwaki, H.; Ninomiya, M.; Adachi, S.; Saito, A.; Takasaki, K.T.; Tanaka, T.; Tsurumi, K.; Okuno, M.; Tomita, E.; et al. Prevention of Second Primary Tumors by an Acyclic Retinoid, Polyprenoic Acid, in Patients with Hepatocellular Carcinoma. Hepatoma Prevention Study Group. *N. Engl. J. Med.* **1996**, *334*, 1561–1567, doi:10.1056/NEJM199606133342402.
11. Muto, Y.; Moriwaki, H.; Saito, A. Prevention of Second Primary Tumors by an Acyclic Retinoid in Patients with Hepatocellular Carcinoma. *N. Engl. J. Med.* **1999**, *340*, 1046–1047, doi:10.1056/NEJM199904013401315.
12. Tabata, Y. Quantitative Screening of Geranylgeranoic Acid in Selected Plant-Based Foods Using LC/MS/MS. *Front. Nutr.* **2025**, *12*, doi:10.3389/fnut.2025.1652270.
13. Shidoji, Y.; Ogawa, H. Natural Occurrence of Cancer-Preventive Geranylgeranoic Acid in Medicinal Herbs. *J. Lipid Res.* **2004**, *45*, 1092–1103, doi:10.1194/jlr.M300502-JLR200.
14. Tabata, Y.; Shidoji, Y. Hepatic Monoamine Oxidase B Is Involved in Endogenous Geranylgeranoic Acid Synthesis in Mammalian Liver Cells. *J. Lipid Res.* **2020**, *61*, 778–789, doi:10.1194/jlr.RA119000610.
15. Tabata, Y.; Shidoji, Y. Hepatic CYP3A4 Enzyme Compensatively Maintains Endogenous Geranylgeranoic Acid Levels in MAOB-Knockout Human Hepatoma Cells. *Metabolites* **2022**, *12*, 140, doi:10.3390/METABO12020140/S1.
16. Tabata, Y. Aging-Dependent Shift in Hepatic GGA Biosynthesis: A Proposed Axis Involving MAOB and CYP3A4 in Liver Cancer Susceptibility. **2025**, doi:10.20944/preprints202506.1957.v1.
17. Tabata, Y. Endogenous and Dietary Geranylgeranoic Acid: A Mini Review on Its Role in Hepatic Tumor Suppression. **2025**, doi:10.20944/preprints202507.0370.v1.
18. Tissue Expression of MAOB - Summary - The Human Protein Atlas Available online: https://www.proteinatlas.org/ENSG00000069535-MAOB/tissue (accessed on 25 June 2025).
19. Tissue Expression of CYP3A4 - Summary - The Human Protein Atlas Available online: https://www.proteinatlas.org/ENSG00000160868-CYP3A4/tissue (accessed on 25 June 2025).
20. Tabata, Y.; Uematsu, S.; Shidoji, Y. Supplementation with Geranylgeranoic Acid during Mating, Pregnancy and Lactation Improves Reproduction Index in C3H/HeN Mice. *J. Pet Anim. Nutr.* **2020**, *23*, 1–8, doi:10.11266/jpan.23.1_1.
21. Shidoji, Y.; Okamoto, K.; Sakane, C. A Livestock Feed or a Promoter for Improving Birth Rate Applied to Mammals, a Tranquilizer Applied to Mammals (in Japanese). 2011.
22. Bergström, S.; Carlson, L.A.; Weeks, J.R. The Prostaglandins: A Family of Biologically Active Lipids. *Pharmacol. Rev.* **1968**, *20*.
23. Mitake, M.; Ogawa, H.; Uebaba, K.; Shidoji, Y. Increase in Plasma Concentrations of Geranylgeranoic Acid after Turmeric Tablet Intake by Healthy Volunteers. *J Clin Biochem Nutr* **2010**, *46*, 252–258, doi:10.3164/jcbn.09-109.
24. Mitake, M.; Shidoji, Y. Geranylgeraniol Oxidase Activity Involved in Oxidative Formation of Geranylgeranoic Acid in Human Hepatoma Cells. *Biomed. Res. Tokyo Jpn.* **2012**, *33*, 15–24, doi:10.2220/biomedres.33.15.
25. Muraguchi, T.; Okamoto, K.; Mitake, M.; Ogawa, H.; Shidoji, Y. Polished Rice as Natural Sources of Cancer-Preventing Geranylgeranoic Acid. *J. Clin. Biochem. Nutr.* **2011**, *49*, 8–15, doi:10.3164/jcbn.10-110.
26. Iwao, C.; Shidoji, Y. Polyunsaturated Branched-Chain Fatty Acid Geranylgeranoic Acid Induces Unfolded Protein Response in Human Hepatoma Cells. *PLoS One* **2015**, *10*, 1–20, doi:10.1371/journal.pone.0132761.
27. Iwao, C.; Shidoji, Y. Induction of Nuclear Translocation of Mutant Cytoplasmic P53 by Geranylgeranoic Acid in a Human Hepatoma Cell Line. *Sci. Rep.* **2014**, *4*, 4419, doi:10.1038/srep04419.
28. Iwao, C.; Shidoji, Y. Upregulation of Energy Metabolism-Related, P53-Target TIGAR and SCO2 in HuH-7 Cells with P53 Mutation by Geranylgeranoic Acid Treatment. *Biomed. Res. Tokyo Jpn.* **2015**, *36*, 371–381, doi:10.2220/biomedres.36.371.

 doi:10.20944/preprints202506.2134.v3

29. Okamoto, K.; Sakimoto, Y.; Imai, K.; Senoo, H.; Shidoji, Y. Induction of an Incomplete Autophagic Response by Cancer-Preventive Geranylgeranoic Acid (GGA) in a Human Hepatoma-Derived Cell Line. *Biochem. J.* **2011**, *440*, 63–71, doi:10.1042/BJ20110610.
30. Shidoji, Y.; Okamoto, K.; Muto, Y.; Komura, S.; Ohishi, N.; Yagi, K. Prevention of Geranylgeranoic Acid-Induced Apoptosis by Phospholipid Hydroperoxide Glutathione Peroxidase Gene. *J. Cell. Biochem.* **2006**, *97*, 178–187, doi:10.1002/jcb.20627.
31. Cyp3a11 Gene Expression - Gene - NCBI Available online: https://www.ncbi.nlm.nih.gov/gene/13112/?report=expression (accessed on 25 June 2025).
32. Huttlin, E.L.; Jedrychowski, M.P.; Elias, J.E.; Goswami, T.; Rad, R.; Beausoleil, S.A.; Villén, J.; Haas, W.; Sowa, M.E.; Gygi, S.P. A Tissue-Specific Atlas of Mouse Protein Phosphorylation and Expression. *Cell* **2010**, *143*, 1174–1189, doi:10.1016/j.cell.2010.12.001.
33. Najafi, A.; Amidi, F.; Sedighi Gilani, M.A.; Moawad, A.R.; Asadi, E.; Khanlarkhni, N.; Fallah, P.; Rezaiian, Z.; Sobhani, A. Effect of Brain-Derived Neurotrophic Factor on Sperm Function, Oxidative Stress and Membrane Integrity in Human. *Andrologia* **2017**, *49*, 1–10, doi:10.1111/and.12601.
34. Tan, X.; Zhao, L.; Tang, Y. The Function of BDNF and Its Receptor in the Male Genitourinary System and Its Potential Clinical Application. *Curr. Issues Mol. Biol.* **2022**, *45*, 110–121, doi:10.3390/cimb45010008.
35. Safari, H.; Khanlarkhani, N.; Sobhani, A.; Najafi, A.; Amidi, F. Effect of Brain-Derived Neurotrophic Factor (BDNF) on Sperm Quality of Normozoospermic Men. *Hum. Fertil. Camb. Engl.* **2018**, *21*, 248–254, doi:10.1080/14647273.2017.1346301.
36. Nakamura, N.; Shidoji, Y.; Moriwaki, H.; Muto, Y. Apoptosis in Human Hepatoma Cell Line Induced by 4,5-Didehydro Geranylgeranoic Acid (Acyclic Retinoid) via down-Regulation of Transforming Growth Factor-Alpha. *Biochem. Biophys. Res. Commun.* **1996**, *219*, 100–104, doi:10.1006/bbrc.1996.0188.
37. Nakamura, N.; Shidoji, Y.; Yamada, Y.; Hatakeyama, H.; Moriwaki, H.; Muto, Y. Induction of Apoptosis by Acyclic Retinoid in the Human Hepatoma-Derived Cell Line, HuH-7. *Biochem. Biophys. Res. Commun.* **1995**, *207*, 382–388.
38. Teletin, M.; Vernet, N.; Ghyselinck, N.B.; Mark, M. Roles of Retinoic Acid in Germ Cell Differentiation. *Curr. Top. Dev. Biol.* **2017**, *125*, 191–225, doi:10.1016/bs.ctdb.2016.11.013.
39. Endo, T.; Mikedis, M.M.; Nicholls, P.K.; Page, D.C.; de Rooij, D.G. Retinoic Acid and Germ Cell Development in the Ovary and Testis. *Biomolecules* **2019**, *9*, 775, doi:10.3390/biom9120775.
40. Speroff, L.; Ramwell, P.W. Prostaglandins in Reproductive Physiology. *Am. J. Obstet. Gynecol.* **1970**, *107*, 1111–1130, doi:10.1016/0002-9378(70)90638-1.
41. Weissenrieder, J.S.; Reilly, J.E.; Neighbors, J.D.; Hohl, R.J. Inhibiting Geranylgeranyl Diphosphate Synthesis Reduces Nuclear Androgen Receptor Signaling and Neuroendocrine Differentiation in Prostate Cancer Cell Models. *The Prostate* **2019**, *79*, 21–30, doi:10.1002/pros.23707.
42. Pont, A.; Williams, P.L.; Azhar, S.; Reitz, R.E.; Bochra, C.; Smith, E.R.; Stevens, D.A. Ketoconazole Blocks Testosterone Synthesis. *Arch. Intern. Med.* **1982**, *142*, 2137–2140.
43. Domosławska, A.; Zduńczyk, S. Reversible Infertility in Male Dog Following Prolonged Treatment of Malassezia Dermatitis with Ketoconazole. *Acta Vet. Scand.* **2021**, *63*, 50, doi:10.1186/s13028-021-00616-9.
44. Pont, A.; Graybill, J.R.; Craven, P.C.; Galgiani, J.N.; Dismukes, W.E.; Reitz, R.E.; Stevens, D.A. High-Dose Ketoconazole Therapy and Adrenal and Testicular Function in Humans. *Arch. Intern. Med.* **1984**, *144*, 2150–2153.