Understanding emergency contraceptive mechanisms of action: Computational molecular modeling of the progesterone receptor against progesterone receptor modulators

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Personal Section

Last year, I studied AP Chemistry and became the only female member of the tech club. Never did I imagine that the collision of these two fields would become my greatest frustration and my most exciting ambition. Learning about the evolution of molecular research, I marveled at how much chemoinformatics has advanced in the past decades. Molecular models were initially created as ball-and-stick figures. Today, we can replicate 3D structures with their surface properties and intermolecular forces. The accuracy of computer modeled ligand-receptor-mediated interactions leaves me awestruck, as I originally thought this knowledge was out of human grasp. The transformation of abstract understanding into concrete principles excites me. My research has given me both answers and more questions. And I learned that sometimes, using an unconventional method to solve a research problem gives the answers we cannot find with conventional methods. The best path is not always the obvious one in the world of research.

After two years of literature review exploring the biological aspects of post-coital contraception, the lack of understanding of the different efficacy of two compounds invoked my curiosity. At the Emergency Contraception Jamboree in New York, I spoke with many leading researchers who offered me the opportunity to study the social implications of emergency contraception; however, I wanted to study the biochemistry and mechanisms of action. Stepping back from the political and social turmoil surrounding this women's health issue, I wanted to take a molecular approach to analyzing emergency contraception. Inspired by a study in which the activity of Dilantin was analyzed using computational molecular docking, I selected a computational approach. Recognizing that in-silico methods pose no ethical issues and save time, I set out to use 3D modeling to examine emergency contraceptive compounds, utilizing a non-controversial method to study a politically controversial area of biochemistry. Initially, I had

independently found a mentor at a research facility at a university in New York. I began to familiarize myself with the Linux Operating System as well as the Hex Docking program I planned to use at the lab. Because there were time constraints interfering with my collaboration with my mentor and the Hex Docking program was experiencing a glitch that would take months to fix, I independently located Dr. Denton Hoyer at Yale University during a tour of the Molecular Discovery Center, a center that conducts research in drug discovery and computational molecular modeling. We collaborated to execute the computational molecular modeling via the Molecular Operating Environment program. Despite a hiccup with my first lab, I believed in my research and its potential future implications in the fields of contraceptive development and computer modeling, so I vigorously sought out a new mentor to aid in my project. In the collaborative research world, there is always someone willing to help; it just takes a proactive researcher to take the first step in creating the relationship. With my research I hope to give women a reliable, less politically divisive, effective emergency contraception to prevent unintended pregnancy. This research clarified my love of science and desire to utilize scientific and mathematical methods to offer understanding and solutions to global issues.

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Abstract

More than half of all pregnancies in the United States are unintended. Emergency contraception is a postcoital contraception that allows women the possibility of preventing pregnancy in cases of unanticipated exposure. There are two emergency contraceptive pills: levonorgestrel (LNG) and ulipristal acetate (UPA). UPA is more effective at preventing pregnancy than LNG and works effectively later in the cycle, yet the reason for this difference in efficacy is unknown. As progesterone receptor modulators, these progestins interact with the progesterone receptor (PR) to suppress ovulation and reduce endometrial receptivity. Therefore, my goal was to determine whether the difference in efficacy between these two compounds is related to the differential interactions of these two compounds with the PR. To do so, we used both an examination of X-ray co-crystals of the receptor with the ligands and *computational modeling,* also known as ligand docking techniques, a fairly new technology that models interactions of small molecules and macromolecular targets via computational methods. The Molecular Operating Environment structure-based-design modeling program simulated the interaction of LNG, UPA and the abortifacient drug mifepristone with the progesterone receptor. It was found that UPA's displacement of helix 12 on the PR is a potential explanation for UPA's superior efficacy to LNG in preventing pregnancy, suggesting helix 12 displacement is key to successful PR antagonism. Moreover, a further examination of available crystals of the PR in complex with various agonists and antagonists suggests the need for the determination of the APO structure, or unoccupied structure, of the progesterone receptor in order to facilitate further structure-based studies.

Review of Literature

More than half of all pregnancies in the United States are unintended [23]. While some of these pregnancies are due to birth control method failures, most are due to unanticipated exposure. *Emergency contraception* is a postcoital contraception that allows women the possibility of preventing pregnancy in such cases.

Currently, there are two types of FDA-approved emergency contraception: the copper-containing intrauterine device (IUD) and oral emergency contraceptive pills. The most effective method for emergency contraception is the IUD at 99.9%. However, the hormonal pills are far more widely used, at about 90% for women who are at risk for pregnancy [20], because they are more easily accessible, more affordable, convenient, free of adverse side-effects and do not require after-care [8, 24]. While the outcomes of emergency contraception are well-documented, their mechanism(s) of action remain a matter of discussion.

Due to the gap in knowledge regarding emergency contraceptive pill efficacy, my study focuses on the mechanism of action of emergency contraceptive pills. Emergency contraceptive pills are believed to prevent pregnancy by inhibiting or delaying ovulation, thereby preventing fertilization. The two available emergency contraceptive pills levonorgestrel (LNG) and ulipristal acetate (UPA), act by binding with progesterone receptors (PR). While action at other receptors is possible, the progesterone receptor actions are considered to be the most important mechanism of action. Interestingly, UPA has been shown to be more effective than LNG, halving the risk of pregnancy in comparison to LNG [10]. Therefore, my study aims to determine whether the difference in efficacy between these two compounds is related to the differential interactions of these two compounds with the PR. The methods included both an examination of X-ray co-crystals of the receptor with the ligands as well as *computational modeling,* or ligand

docking techniques, a fairly new technology that models interactions of small molecules and macromolecular targets via computational methods.

The biological effects of emergency contraceptive pills vary according to the time of the menstrual cycle when the drug is administered. Conception is possible during a six-day fertile window of the typical 28-35 day cycle. The luteinizing hormone (LH) surge period, which occurs as a positive feedback response to estrogen rising and eventually peaking around day 12 of the cycle, stimulates ovulation with the release of an ovum from a follicle within 36 hours [7]. Thus, understanding how emergency contraceptive compounds interact with the biological hormones on different days of the menstrual cycle is critical for understanding the mechanism of action of emergency contraception.

Progesterone Receptors (PRs)

Progesterone is an endogenous steroid hormone that plays an important role in oocyte release from the ovary by facilitating the LH surge. It is also responsible for differentiation of the endometrium and implantation [7]. The actions of progesterone receptor modulators in target tissues are mediated by the PR.

To activate the PR, ligands or compounds that bind to the PR first induce a conformational change of the receptor, thereby resulting in a loss of heat shock proteins and receptor dimerization to allow DNA binding and transcription. In contrast, PR antagonists make the receptor transcriptionally-inactive by inducing a modified conformation of the receptor [5]. Given its role in pregnancy, the PR is a protein of interest with respect to developing contraceptive compounds.

Progesterone Receptor Modulators

Progesterone receptor modulators represent the class of hormones that interacts with the progesterone receptor at the ligand-binding-domain, or LBD. PR modulators range from full agonists to full antagonists, yet there is growing interest in research on selective progesterone receptor modulators, which exhibit mixed profiles of partial agonist and partial antagonist action on the progesterone receptor [13]. Currently, full antagonists, such as mifepristone, are used to induce medical abortion. Emergency contraceptive pills are progestins or antiprogestins. A likely mechanism to the action of the progesterone receptor is movement of helix 12. Previous studies have indicated that displacement of helix 12 on the progesterone receptor is crucial for progesterone receptor antagonism [18]. Thus, the two progesterone receptor antagonists analyzed in my study, mifepristone and ulipristal acetate, were expected to demonstrate helix 12 displacement. The three progesterone receptor modulators used in my study were: mifepristone, levonorgestrel, and ulipristal acetate.

Mifepristone (RU486). A strong progesterone receptor antagonist (antiprogestin), mifepristone is prescribed in a 200 mg dose followed by misoprostol, a prostaglandin that causes uterine contractions, to induce safe and effective medical abortion for up to 70 days from the last menstrual period [1]. By binding to the progesterone receptor with a greater affinity than progesterone, mifepristone blocks the actions of progesterone on the progesterone receptor to increase uterine sensitivity to prostaglandins, resulting in uterine contractions, cervical softening, and dilation and shedding of the decidua. Followed by the administration of misoprostol, mifepristone ends unwanted pregnancies approximately 97% of the time [22].

Levonorgestrel (LNG). Unlike mifepristone, emergency contraceptive pills are not abortifacient. The most commonly used ECP is levonorgestrel, which works by delaying or inhibiting ovulation. As a progestin, levonorgestrel interacts with the progesterone receptor to

suppress the release of luteinizing hormone via a negative feedback loop on the hypothalamus with luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in the inhibition of ovulation [16]. Administered at 1.5 mg, it is commonly seen under the brand Plan B or Plan B OneStep and is available over the counter in the United States to women of all ages. The accepted effectiveness of levonorgestrel is based on World Health Organization results, which showed a 95% prevention of expected pregnancies when taken within 24 hours.

The window of efficacy for LNG is 72 hours, beginning after the selection of the dominant follicle and ending before LH begins to rise [14]. If taken when LH has already started to rise, levonorgestrel will not prevent ovulation or affect the endometrium, thus, levonorgestrel is only effective if taken before the LH peak [8, 15].

Ulipristal acetate (UPA). Ulipristal acetate (UPA) is a novel orally active selective progesterone receptor modulator, with antagonistic and partial agonist effects (a progesterone agonist/antagonist). This mixed profile of both agonist and antagonist action depends on the chemical profile of the selective progesterone receptor modulator. In some cases, weak agonists function as antagonists by their ability to bind tightly to the PR, yet induce no conformational change. In this case, physically blocking the ability of progesterone to bind to the PR serves as an antagonistic mechanism.

Thus, UPA can block the action of progesterone receptors or bind to the receptor in order to trigger a response, and is a chemical and pharmacological analog to mifepristone. Similar in structure to mifepristone, both UPA and mifepristone have a large phenylamine group, which levonorgestrel does not have (Figure 1, overleaf). Based on this difference, we hypothesize this phenylamine group likely contributes to antagonistic activity on the PR by interfering with binding.

UPA functions by binding to progesterone receptors in the uterus and corpus luteum. This action competes with progesterone to occupy the receptor and block the effects of progesterone, which is crucial for pregnancy to occur. Its primary mechanism of action is inhibition or delay of ovulation [4]. Marketed as a 30 mg tablet to be taken within 120 hours of intercourse, UPA is sold under the brand name Ella, and women who intake UPA at 30 mg between 48 and 120 hours after unprotected sex show pregnancy rates of 2.1% [9].

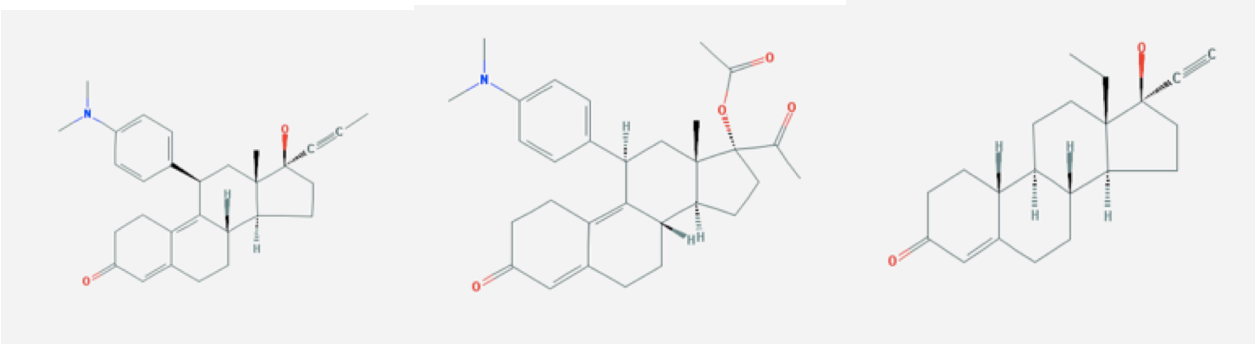

Figure 1. Molecular Structures of Mifepristone (1A), UPA (1B), and LNG (1C). UPA (middle) and mifepristone (left) are nearly identical in structure with the exception that UPA possesses one more carbon, 2 more hydrogens, and 2 more oxygens. LNG (right) lacks the phenyl group that UPA and RU486 both possess. (PubChem).

Comparison of ulipristal acetate and levonorgestrel. In comparison to LNG, UPA can be used up to 120 hours following unprotected sex without losing its efficacy, while levonorgestrel can only be used up to 72 hours following unprotected sex and loses efficacy with time [3]. When administered before the onset of the LH surge, UPA delays the LH peak and ovulation, as does LNG [4, 6]. Administered after the onset of the LH surge yet before the LH peak (at a time when LNG is no longer effective), UPA still produces a significant effect by delaying ovulation approximately five days. UPA and LNG are ineffective at preventing follicular rupture the day of the LH peak [4].

While both pills' mechanism of action is to interfere with ovulation, UPA also has potential to produce a post-ovulatory effect on the receptivity of the endometrium, thickening it

and thereby preventing the implantation of a blastocyst, yet UPA does not disrupt implantation or affect the implanting embryo [2]. In contrast, LNG produces minimal to no changes in the endometrium [14, 25].

Most importantly, UPA is known to be more effective at preventing pregnancy than LNG. UPA reduces the risk of pregnancy by nearly 50% compared to levonorgestrel in women who received emergency contraception within 120 hours [10]. However, it is currently unknown why UPA as a compound is more effective at preventing pregnancy than LNG. Therefore, this study focuses on determining the mechanism responsible for UPA's increased efficacy.

Although both compounds are used in the prevention of pregnancy through suppression of ovulation and the LH peak, they differ in chemical properties (Table 1). Because both pills

Table 1. Chemical Details of LNG, UPA, and Mifepristone. (Berenblum, 2015).

Compound Properties	Levonorgestrel (LNG)	Ulipristal Acetate (UPA)	Mifepristone (RU486)
Molecular Formula	C_{21} H_{28} O_2	C_{30} H_{37} N O_4	C_{29} H_{35} N O_2
Hydrogen Bond Acceptors	2	5	3
Hydrogen Bond Donors	1	0	1
Rotatable Bonds	1	5	2
Topological Surface Area Å	37.3	63.68	40.54
Molecular Weight	312.21 g/mol	475.27 g/mol	429.27 g/mol
PR Agonist Affinity nM	11.0	<7.0	9.0
PR Antagonist Affinity nM	N/A	9.7	9.0
Hormone Class	Progestin (Agonist)	Antiprogestin with mixed profile (Partial Agonist, Partial Antagonist)	Antiprogestin (Antagonist)

work by the same mechanism on the same receptor, with one being more effective than the other, the differences in compound properties and the effect on receptor binding is a likely explanation for varying efficacy.

Typically, studies on emergency contraception are conducted by analyzing the percentage of follicular ruptures prevented by the drug. Women who participate in emergency contraception studies are often tracked for their sexual activity, timing and dosage of emergency contraception intake, and incidence of pregnancy, yet this does not give researchers an understanding of how the drug interacts at specific locations on the receptor. This study seeks to take a molecular approach rather than an *in vivo* approach to emergency contraceptive compounds by analyzing the molecular interactions of the compounds with the progesterone receptor as simulated by a computational molecular environment. Because the mechanism of action of emergency contraception is not well understood, the interaction of LNG and UPA with the PR was analyzed in order to gain a better understanding of the reason for emergency contraceptive pills' efficacy on a molecular level. The binding of each drug to the progesterone receptor was examined from published crystallographic studies as well as modeling of the interactions of the drugs.

Computational Molecular Modeling

Drug activity is analyzed via the molecular binding of one molecule to the pocket of a macromolecular target [21]. The molecule that binds to the pocket is called the ligand, while the larger target molecule is the receptor [12]. The interaction of the ligand and receptor must exhibit geometric and chemical complementarity to induce successful drug activity [21].

Many drug discovery programs use the method of computational molecular docking and modeling [11]. Biophysical techniques, such as x-ray crystallography, have led to a broad array of known protein structures. Due to the increased number of proteins with known three-dimensional structures and the rising availability of protein data banks, computational methods are becoming more prevalent in research [12]. However, because determining crystal structures

through x-ray crystallography produce a single snapshot of a protein structure in its lowest energy form, the structure does not reflect all energy states of the protein.

Computational molecular modeling determines whether a selected ligand is able to dock into the binding site of a protein [21]. In other words, the interaction of the ligand and receptor can be viewed as a glove and hand fit that would describe the "best-fit" orientation of a small molecule that lodges into a protein of interest. Docking programs endeavor to achieve the correct orientation of the fit between the small molecule and macromolecule, aiming to achieve an optimized conformation for both molecules such that the free energy is minimized, thus maintaining energetic favorability of the interaction [21].

In addition to revealing orientation, docking studies are used to identify the structural features, or *residue contacts*, that are important for a successful drug interaction. When a small molecule binds to a receptor, it contacts specific locations called sequence segments, on the receptor. Understanding the contact responsible for a specific mechanism of action of a molecule allows researchers to understand why a molecule induces a specific effect when it binds to a receptor. Ligand binding to a receptor alters the *chemical conformation*, or 3-D shape, of the molecule to induce an effect. The orientation of the two molecules involved in the interaction may affect the type of signal produced, antagonist or agonist. It is important to understand, however, that while computational docking can inform us as to the geometry of binding, it is very poor at giving us an idea of how tightly the ligand binds with the receptor. This is evident in the lack of correlation of the docking score with experimentally measured binding affinities.

Because molecular docking programs predict and simulate the interaction of a drug compound with a receptor, this method was used to model the progesterone receptor modulators of interest with the progesterone receptor ligand-binding-domain. The modeling aided in the

recognition of differences in interactions and their consequent effects on the ability to prevent pregnancy. Because the isoforms have identical ligand-binding-domains, each compound was docked to the ligand-binding-domain of the progesterone receptor. The *pose* or *orientation* of binding of the molecules was visualized. Both agonists, progesterone and levonorgestrel, were expected to show similar interactions, while the two antagonists, mifepristone and ulipristal acetate were expected to show different interactions from the agonists with a focus on displacement of helix 12. *This study is the first of its kind to dock and compare progesterone, levonorgestrel, mifepristone, and ulipristal acetate in one study.*

Hypotheses

H_0: The pose of the antagonists ulipristal acetate and mifepristone with the progesterone receptor will be the same as the agonists levonorgestrel and progesterone.

H_1: The pose of ulipristal acetate bound with the progesterone receptor and mifepristone bound with the receptor will be different than the pose and residue contacts of levonorgestrel bound with the progesterone receptor.

H_2: As antagonists, ulipristal acetate and mifepristone will displace helix 12, while levonorgestrel will not.

Objectives

1. Dock ulipristal acetate, levonorgestrel, mifepristone, and progesterone to the progesterone receptor within the top five poses.
2. Compare the best pose for each docking interaction to determine the geometry of the fit to the ligand-binding-domain of the progesterone receptor.
3. Determine whether helix 12 displacement occurs in the progesterone receptor for the antagonists.

Methods

The Molecular Operating Environment (MOE; Chemical Computing Group, Quebec, Canada) molecular modeling software was utilized to dock the small molecular emergency contraceptive compounds into the ligand-binding-domain of the target receptor: the progesterone receptor. The MOE software is able to graphically visualize crystallographically determined structures, analyze them, and computationally dock small molecule ligands into protein receptors, such as the progesterone receptor. This modeling system was used to visualize the 3D structures of ulipristal acetate, mifepristone, levonorgestrel, and the progesterone receptor ligand-binding-domain.

The study involves the use of four crystallographic structures reported in the Protein Data Bank (rcsb.org). These structures are 1A28 (Progesterone), 3D90 (Levonorgestrel), 4OAR (Ulipristal acetate), and 2W8Y (Mifepristone) with the progesterone receptor. The structures were imported, the water molecules were removed, and the side chains were appropriately charged using an internal docking prep software called LigPrep. The Merck Molecular Force Field (MMFF94) was used for docking. All protein crystal structures were reduced to their single monomers, which were then aligned and superposed for analysis of alpha chain and helix movements as well as ligand superposition. This superposition showed overall very similar alpha backbone and ligand overlay.

Using data on inner-atomic distances and angle histograms, the probabilistic contact potentials feature of MOE generated likely contact locations. Pose was determined as well using geometric shape complementarity and the physicochemical interactions between the small molecule and the macromolecular target. Using ligand-receptor docking under structure-based design in MOE, the top five poses for each interaction were considered in the results. The top

five poses were poses that minimized the energy of the interaction to represent a thermodynamically favorable interaction. Docking, while not predictive of bioactivity per se, may provide insight into the relevant bioactive conformations of both the protein and its ligand, and therefore, serve to rationalize bioactivity.

Results and Discussion

Modeling

Pose. The modeling and graphical inspection of superposed crystal structures showed little conformational change on the alpha backbone for most of the receptor for each of the drugs. In other words, all ligands are accommodated in reasonable geometry (Figure 2A). This finding is not too surprising for the two agonists, progesterone and levonorgestrel. Although the ligands are different and have differing biological implications, the overlay of the ligands is similar even for the antagonists, ulipristal acetate and mifepristone. The very similar overlay of all ligands was surprising, as one hypothesis would be that significant protein movement would occur due to the large phenyl ring in both antagonist drugs. The phenyl ring would likely clash with an overlaying helix, known as helix 12. On further examination, clashes with the mifepristone phenyl ring were seen with the methionine 909 residue (Figure 2B).

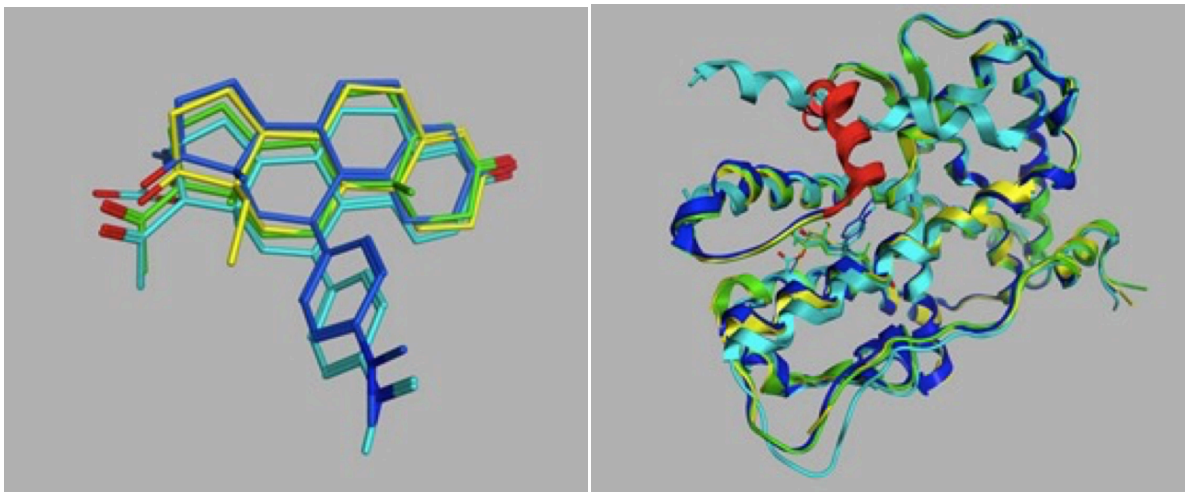

Figure 2. Overlay of Ligands (2A) and Overlay of Receptors (2B). Progesterone (green), levonorgestrel (yellow), UPA (cyan), and mifepristone (blue) have very similar backbone structures. UPA (cyan) and mifepristone (blue) both have the phenyl group sticking out at the bottom, demonstrating their similarity as progesterone antagonists. Pictured at right, progesterone, levonorgestrel, UPA, and mifepristone show very little conformational change on the receptor structure. Helix 12 is depicted in red and is only displaced by UPA. (Berenblum, 2015).

An overlay of the receptors shows displacement of helix 12 by the antagonistic UPA, not mifpristone (Figure 3). Although expected that both antagonists, UPA and mifepristone, would displace helix 12, as it has previously been hypothesized that helix 12 displacement is crucial to progesterone receptor antagonism [19], it is possible that UPA was more capable than mifepristone in overcoming the energy barriers to displace helix 12. The fact that the determined crystal structure of mifepristone bound to the PR is likely a high-energy state explains the inability of mifepristone to show helix 12 displacement. The crystal was obtained by initially crystallizing the receptor with progesterone, then soaking in the mifepristone antagonist to replace the natural hormone. It is likely that close monomer crystal contact packing prevented the protein from moving, thus forcing the antagonist to assume a high-energy state. Normally, a single conformation of lowest energy is seen from crystallographic studies, whereas the receptor is an ensemble of multiple structure states. The balance of these states determines the action of the receptor in triggering nuclear transcription and normal hormone or drug action.

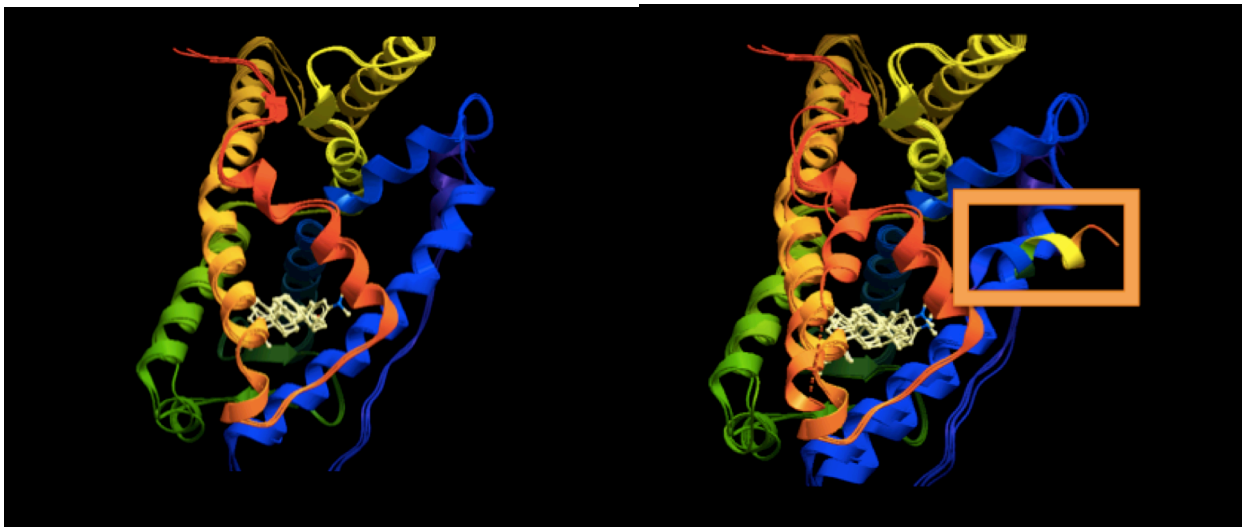

Figure 3. Overlay of Interactions of Mifepristone, LNG, and Progesterone (left) and Overlay of All Interactions (right). Pictured on the left is an overlay of the progesterone receptor interaction with levonorgestrel, mifepristone, and progesterone. Depicted in the right is an overlay of all four interactions, including ulipristal acetate. UPA displaces helix 12, in the orange box, unlike the other compounds. (Berenblum, 2015).

We hypothesize, therefore, that the important helix 12 movement would occur for antagonists, such as mifepristone and ulipristal acetate, and that helix 12 displacement is essential to effective PR antagonism and the consequent prevention of pregnancy. Moreover, because there appears to be no available crystal structure of mifepristone in complex with the PR in its antagonistic conformation, this project sheds light on the need for the availability of the APO, or unoccupied, structure of the PR. Solving the APO structure would facilitate future computational research on the interaction of agonists, antagonists, and mixed profile progestins with the PR.

To address the fact that x-ray crystallography only shows one snapshot of a structure in its lowest energy form, future research calls for analyzing the compounds in more dynamic states of their structure. Nuclear magnetic resonance would be able to determine the structure of each compound at room temperature when energy barriers are small, in which case, the compounds would be in a higher energy structure and perhaps be more likely to overcome energy barriers to induce a conformational change on the receptor. Additionally, future research could involve re-modeling the interactions under a molecular dynamics study. Molecular dynamics would reveal an ensemble of higher energy state snapshots of the structure and show greater conformational changes by the agonists and antagonists on the receptor.

The main limitation of a computer modeling study is that it is a prediction method. This study used a computational method to generate the testable hypothesis that helix 12 displacement on the PR is crucial to PR antagonism and effective prevention of pregnancy. Moreover, this study presents the need for future research to solve the APO structure of the progesterone receptor in order to conduct further computational modeling studies on realistic PR structures and to serve as a reference for the graphical analysis of the crystallographic structures.

Conclusion

This study is the first of its kind to test 3D models of levonorgestrel, ulipristal acetate, progesterone, and mifepristone to analyze the interaction of these progesterone receptor modulators with the progesterone receptor. This research gives insight into how progesterone receptor modulators dock to the ligand-binding-domain of progesterone receptors, while revealing the need for an unoccupied, high resolution structure of the progesterone receptor that can be used in future computational modeling studies. We now believe that helix 12 displacement is crucial to progesterone receptor antagonism and consequently, effective prevention of unintended pregnancy. This is a hypothesis that should be tested *in vivo* in order to give insight into how progesterone antagonists and the next generation of emergency contraceptives can effectively inhibit the action of progesterone on its receptor to prevent pregnancy. In effect, a new emergency contraceptive compound with greater efficacy will help reduce the occurrence of unplanned pregnancy, the need for abortion, and will likely satisfy the over 120 million women around the world who report an unmet need for contraception. According to the United Nations, "the coming decades will see a record number of young people entering prime reproductive ages, requiring the means to prevent unintended pregnancy." In fact, the total number of women of reproductive age will increase by about 144 million women between 2015 and 2030, or in other words, by 45 percent in all major areas besides Europe [20]. As stated by the United Nations, "achieving universal access to sexual and reproductive health care for women and adolescents remains one of the most critical components of the unfinished agenda of the Program of Action of the International Conference on Population and Development." Understanding the molecular interactions of emergency contraception is a step towards achieving this goal.

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