

RU 486 AND ITS ACTION

What has come to be known as the “French abortion pill,” RU 486, is a steroid that has a high affinity for the progesterone receptor. It is the first available “antiprogesterone” and has been used successfully as a medical alternative for voluntary early pregnancy interruption. It is also effective in treating endometriosis, uterine fibroids, breast cancer, and other hormone related conditions. Recent research has provided some insight into the cellular and molecular mechanism of action of both RU 486 and progesterone.

Progesterone is essential for maintenance of the uterine lining during implantation and pregnancy. RU 486, like progesterone and other steroids (Fig. 1), is lipid soluble and thus able to penetrate the plasma membrane and enter the cytoplasm of the target cell. Once inside the cell, both progesterone and RU 486 interact with specific progesterone-receptor proteins in the nucleus. The complex consists of two parts, one protein which has a binding site for progesterone, and a second protein, called heat shock protein (hsp) (Fig. 2). Both RU 486 and progesterone compete for the same binding site on the progesterone-receptor, but RU 486 actually has a higher affinity for the receptor than progesterone. When progesterone is bound to the receptor, the progesterone-receptor complex is able to recognize and bind to a specific site on DNA in the nucleus, thereby initiating transcription of specific genes (Fig. 2A) that code for proteins necessary for the pregnancy to continue. When RU 486 is bound instead of progesterone, the receptor-RU 486 complex does not trigger the normal response. It is thought that hsp may not separate so the RU 486-receptor complex cannot interact properly with the DNA (Fig. 2C) or, if it does, the complex may be altered in some way as to interfere with the transcription process (Fig. 2B). RU 486 is an antiprogesterone, since it occupies the binding site of the receptor without triggering a cellular response.

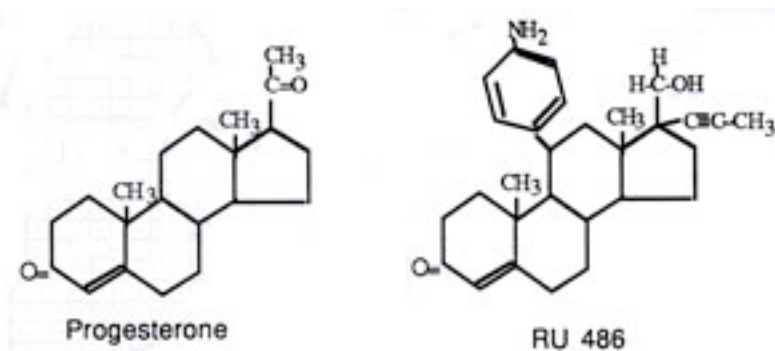


Fig. 1. Structure of progesterone and RU 486.

RU 486 INTERRUPTS PREGNANCY

It was hypothesized that a short interruption in the supply of progesterone to the pregnant human uterus would cause irreversible damage to the lining, leading to a sloughing off of the uterine lining and termination of the pregnancy. Clinical trials and experience for several years in different countries have confirmed this hypothesis. In addition, the administration of RU 486 has been found to produce an increase in the secretion of prostaglandins, hormone-like substances that are produced by a variety of animal tissues, including the uterine lining. Prostaglandins in the uterus promote dilation and softening of the cervix.

RU 486 has been used successfully for pregnancy termination by more than 100,000 women in France, and is being used in Great Britain and Sweden. The standard treatment, RU 486 pills followed by prostaglandin injection, is 95.5 percent effective. A new “pill only” treatment involving RU 486 pills followed by prostaglandin injection, is even more effective. The new RU 486-prostaglandin treatment could be particularly useful in underdeveloped countries where surgical facilities are limited; most women would be able to avoid instrumental intervention, with its risk of infection, cervical injury, and uterine perforation. In addition, this treatment will provide privacy to all women. The Supreme Court has ruled that RU 486 can be brought into the US for personal use. It has been licensed to the non-profit US Population Council and testing is underway. The Clinton administration is supporting the development of this drug for pregnancy termination, treatment of certain cancers, and many other medical uses related to progesterone action.

Key
 P = Progesterone
 P-R = Progesterone Receptor
 hsp = Heat Shock Protein
 RU = RU 486

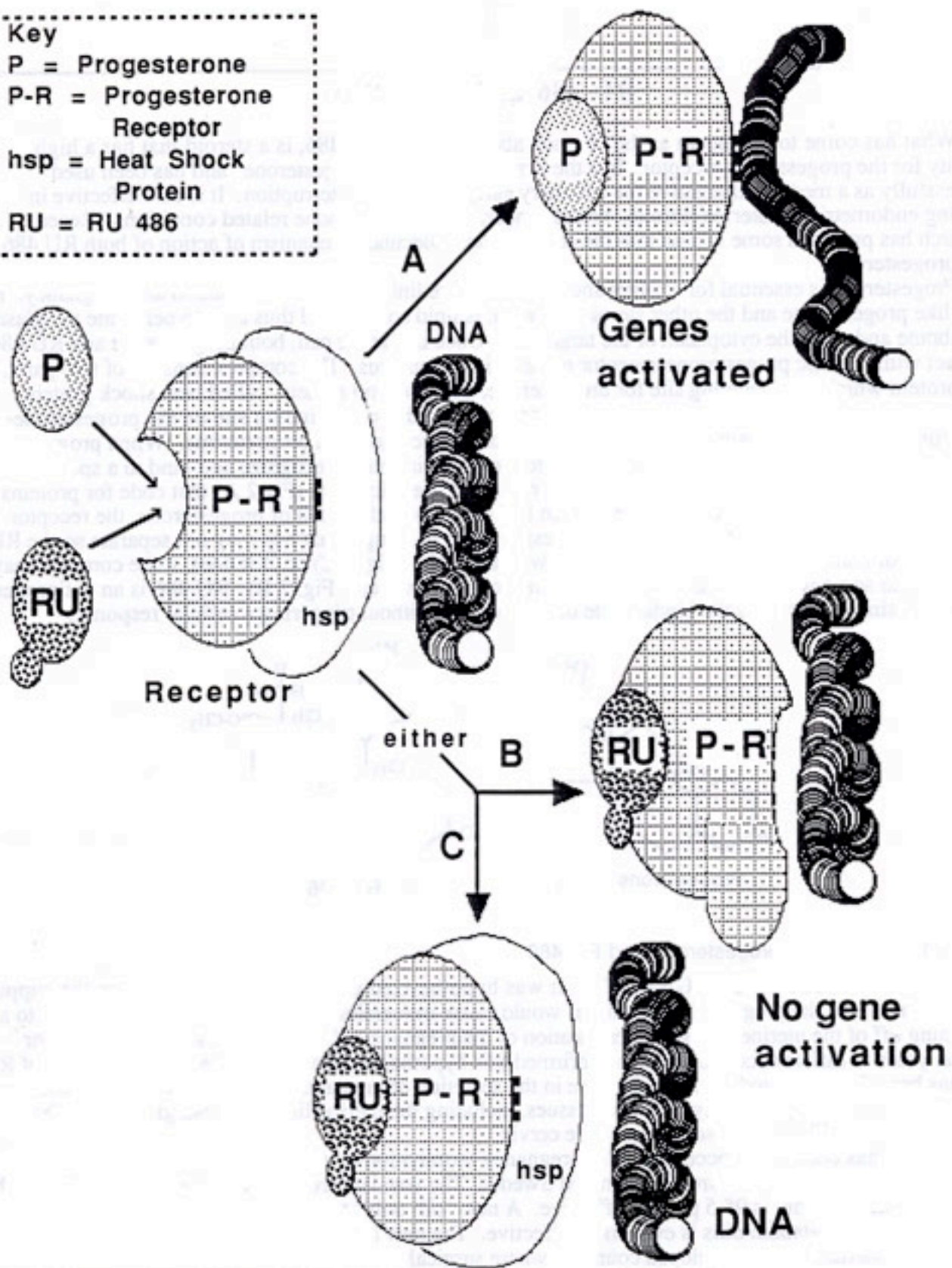


Fig. 2. Mechanisms of progesterone and RU 486 action. Both progesterone and RU 486 can bind to the progesterone-receptor-hsp complex. When progesterone binds to the receptor (top, right), hsp dissociates and the P-R complex binds to a site on the DNA, activating specific genes. When RU 486 binds, the RU 486 complex either changes shape such that it cannot bind properly to the DNA, or it binds so tightly to hsp that hsp remains bound to the complex.