Chapter 21

An animal model for pharmacologic evaluation of the menopausal hot flush

J. W. Simpkins and M. J. Katovich

1. CRITERIA FOR ANIMAL MODELS FOR HUMAN DISEASES

Animal models are extremely important in our efforts to understand human diseases. For obvious ethical reasons, human experimentation is limited in its scope and is heavily dependent upon inferences drawn from case reports, retrospective studies and prospective evaluations using limited sample sizes and strict limits on invasive procedures. Efforts to study the mechanism of diseases and the initial evaluation of their therapy usually require animal experimentation. These animal evaluations allow for the control of a variety of variables, the required sampling of tissues believed to be involved in the disease process and the use of appropriate sample sizes. In this respect, animal experimentation can serve as an indispensable tool for the ultimate resolution of the mechanism of human disease and, as a result, for the development of an appropriate therapy.

The usefulness of an animal model depends upon several basic criteria. First, the animal must be relatively inexpensive, readily available and not require elaborate maintenance conditions. Hence the animal model would be available to investigators interested in a variety of aspects of the disease and who could apply their methodologies to its understanding. Second, the animal species should be genetically homogeneous, a characteristic which reduces the inherent variability of biological data. A persistent problem in many clinical studies is the high variability of the endpoints used in the evaluation of disease states. Finally, the anatomy and physiology of the
tissues, organs and/or organ systems involved in the disease should be well understood in the animal model. The basis of our understanding of pathophysiology is the extent to which we understand the normal function of a system.

Given the basic criteria, the most appropriate animal models are those in which the human disease appears spontaneously. Thus, for example, animal models are available in which hypertension, atherosclerosis, obesity, diabetes mellitus or a variety of tumors develop spontaneously. More often, however, diseases are induced in animals in an attempt to mimic the human syndrome. Numerous disease states can be induced by a variety of experimental manipulations. Induced animals model are available for diabetes mellitus, hypertension, obesity, tumors, Parkinson’s disease, Alzheimer’s disease, etc. While the appropriateness of each of these models is the subject of continuing investigation, there is little question that these animal models have contributed enormously to our understanding of a variety of disease states.

We describe in this report the basis for a preliminary evaluation of an animal model using the rat for the menopausal hot flush. Our primary purpose in developing this animal model was to evaluate the hormonal and endocrine factors which contribute to flushes and to provide a means of effectively testing alternative therapies for the vasomotor syndrome.

2. THE MENOPAUSAL SYNDROME AS A GONADAL STEROID WITHDRAWAL PHENOMENON

The perimenopausal period refers to the time of involution of the ovaries and the various responses of the body to the loss of ovarian steroid secretion1,2. The menopause defines the specific event of the cessation of menses which accompanies the loss of cyclic secretion of ovarian steroids3,4. In response to the loss of ovarian estrogens and progestins, several ‘extragenital’ symptoms appear in most women. These symptoms most often express themselves as hot flushes, perspiration, muscle and joint pain, fatigue, headaches and irritability3,4. Their intensity and frequency vary among women and symptoms do not occur at all in about 25% of menopausal women.

The most frequent and characteristic extragenital symptom of the menopause is the hot flush, an episodic disturbance of thermoregulation characterized by a sensation of heat followed by a sudden spreading flush and perspiration. Of women who experience hot flushes, 82% report that the symptoms last for more than 1 year while 26% experience hot flushes for more than 5 years5. Like the other symptoms of the menopause, hot flushes vary in frequency and intensity among women to such an extent that some never experience hot flushes while others report 20 or more