

A preclinical model of menopause: the ovariectomized female rat

Menopausal symptoms

Menopause is a physiological event due to reduced functioning of the ovaries, resulting in lower levels of estrogen, progesterone and other hormones, marking the permanent end of fertility. Menopause is usually associated with :

- short and mid-term changes :
 - vasomotor changes : hot flushes/ flashes, night sweats, disturbed sleep
 - genital changes : vaginal atrophy, reduced vaginal blood flow inducing lubrication difficulties (vaginal dryness)
 - sexual dysfunction : hypoactive sexual desire disorder, sexual arousal disorder, dyspareunia
- long-term changes :
 - osteoporosis
 - increased risk of depressed mood
 - impaired cognitive functions, including learning and memory

Treatments for menopausal symptoms

Hormonal Replacement Therapy (HRT), consisting in estrogens alone or a combination of estrogens and progestins, is the most common treatment prescribed to menopausal women. However, since 2002, several studies have pointed serious adverse effects, including breast and uterus cancer, and increased risk of stroke, associated with HRT. Alternative treatments represent an urgent medical need.

Experimental model

The ovariectomized female rat is a useful preclinical model for the understanding of the physiopathological events associated to menopause and for the development of new effective therapies.

Model's advantages:

- Since the ovaries are the major source of estrogens, removal of the ovaries mimics an estrogen-deprived state. It is well documented that as women enter menopause, the levels of circulating estrogens decrease (serum estrogen levels fall from 120 pg/mL to approximately 18 pg/mL in post-menopausal women; and from 60 pg/ml to 25 pg/ml in 2 weeks ovariectomized female Sprague-Dawley rat), resulting in a number of physiological changes.
- Ovariectomy in the female rat mimics many post-menopausal physiological modifications, in both phenotypical and histological features.

Pathophysiological features and measurable endpoints:

- Thinning of the epithelium
- Decrease in the number of layers in the stratified epithelium } ⇒ Vaginal atrophy
- Severe degeneration in epithelial architecture
- Decrease in vaginal smooth muscle contractile and relaxation responses to neuropharmacological stimulation,
- Decrease in vaginal blood flow ⇒ Vaginal doppler
- Variations of skin temperature ⇒ Hot flushes / flashes
- Decrease in sexual motivation and behaviour ⇒ Behavioural science

Summarized methodology:

Adult non-pregnant female Sprague-Dawley rats are ovariectomized through bilateral upper back-flank incisions. The ovarian bundles are tied off with 3/0 polyester suture and the ovaries removed. The effectiveness of ovarian removal is checked under binocular microscope. The fascia and the skin are closed using 3/0 polyester suture.

Related Pelvipharm bibliography:

Giuliano, F et al., Am J Physiol Regul Integr Comp Physiol. 2001 Jul;281(1):R140-9

Links to applicable experimental skills:

- Administration routes / regimen

- Plasma / urine / tissue collection

- In vivo experiments – anesthetized animals

- * Vaginal atrophy
- * Vaginal blood flow engorgement measurement by Laser Doppler Flowmetry
- * Model of hot flushes / flashes
- * Bladder blood flow

- Behavioural Science

- * Unilevel chamber
- * Unilevel pacing chamber
- * Sexual incentive motivation test
- * Bilevel chamber

- Urodynamic evaluation (anesthetized)

- Urodynamic evaluation (conscious)

- Organ bath studies

- * Rat tissues

- Biochemistry

- * Spectrophotometric assays
- * Protein expression and activity

- Histology/Morphometry

- * Histomorphology
- * Histomorphometry

- Immunohistologie/Immunofluorescence/Confocal microscopy

- * Immunohistology
- * Immunofluorescence
- * Confocal microscopy