

A preclinical model of pre- and peri-menopause : the ovariectomized hormonally primed female rat

Pre- and Peri-Menopausal hormonal status

After puberty, women experience regular ovarian cycles controlled by estrogens and progestogens variations. During the peri-menopause period, the reduced functioning of the ovaries results in lower levels of estrogen, progestogens and other hormones. The peri-menopause period can be associated with the beginning of discomfort symptoms such as:

- 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

Treatments for peri-menopausal symptoms

Hormonal Replacement Therapy (HRT), consisting in estrogens alone or a combination of estrogens and progestins, is the most common preventive treatment prescribed to peri-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 hormonally primed 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.
- The hormonal supplementation can be perfectly adapted to the model and goal of the study
 - The ovariectomized female can be supplemented with doses of estradiol and progesterone restoring normal circulating hormonal levels, comparable to an intact female.
 - The ovariectomized female can be supplemented with low doses of estradiol and progesterone mimicking circulating hormonal levels comparable to the peri-menopausal period
- The ovariectomized hormonally primed female rat mimics many pre- and peri-menopausal physiological modifications, in both phenotypical and histological features.

Measurable endpoints:

- Histological analysis of the genital organs including vagina and uterus ⇒ Vaginal atrophy
- Vaginal smooth muscle contractile and relaxation responses
- Vaginal blood flow during sexual arousal ⇒ Vaginal Doppler
- Variations of skin temperature ⇒ Hot flushes / flashes
- Sexual motivation and behaviour ⇒ Behavioural Science

Summarized methodology:

Adult non-pregnant female Sprague-Dawley rats are ovariectomized bilaterally through a dorsal incision. 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. Hormonal supplementation with estradiol and progesterone is subcutaneously delivered at the appropriate doses.

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 / 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
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