Estradiol

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Estradiol (E2; primarily 17β-estradiol and, to a much lesser extent, 17α-estradiol) is the most potent endogenous estrogen and a key regulator of reproductive and metabolic physiology. Beyond its classical role in reproduction, E2 integrates endocrine, paracrine, and intracrine signals to preserve whole-body energy homeostasis. In metabolic tissues, where estrogen receptor α (ERα) is the predominant isoform, E2 regulates glucose and lipid metabolism, mitochondrial function, fuel utilization, inflammation, and cardiometabolic resilience in a sex- and age-dependent manner, contributing to sexual dimorphism.

Loss of E2 signaling (as in menopause) or its impairment in other physiopathological contexts increases cardiometabolic risk. When initiated within the so-called window of opportunity, estrogen-based hormone replacement therapy (HRT) partially restores metabolic estrogen signaling in post-menopausal women, lowering cardiometabolic risk and reducing inflammation and oxidative stress.

Signaling Facts

- E2 is a C18 steroid derived from tissue-specific conversion of testosterone or androstenedione by aromatase (CYP19A1).
- During reproductive life, the ovary is the primary source of E2; in males and after menopause, extragonadal synthesis (i.e. adipose tissue, bone, brain) determines local availability.
- E2 signals through the nuclear ERα and ERβ to regulate gene transcription
- E2 also elicits rapid non-genomic effects *via* membrane-associated receptors, including the G protein–coupled estrogen receptor (GPER), and other nuclear independent mechanisms.

Physiological Role

- E2 contributes to sexual dimorphism in metabolic disease susceptibility.
- In the hypothalamus, E2 suppresses appetite, increases energy expenditure, and promotes brown adipose (BAT) tissue thermogenesis.

- In the liver, E2 represses gluconeogenesis, limits steatosis, and promotes fatty acid oxidation, reducing susceptibility to insulin resistance and metabolic dysfunction-associated steatotic liver disease (MASLD).
- In skeletal muscle, E2 enhances mitochondrial function and metabolic flexibility.
- In white adipose tissue (WAT), E2 regulates lipid turnover and distribution, promotes *beiging*, and limits inflammation.
- In pancreatic β cells, E2 preserves cell viability and promotes insulin secretion.
- Declining E2 levels after menopause are associated with increased cardiometabolic risk, while appropriately timed HRT improves metabolic outcomes.

Acknowledgments

This work was supported by Pfizer Global NASH ASPIRE Competitive Grant Program (Grant 77230651). The figures were created with BioRender.com.

Declaration of interests

No conflict of interests to declare.

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Figure 1

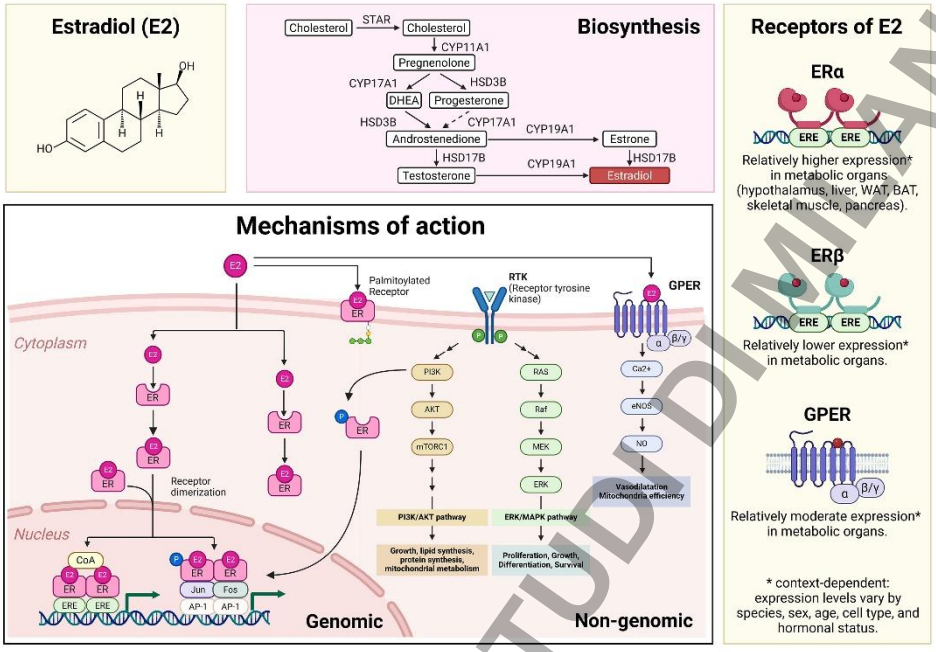

Figure 2