
Environmental Influences on Fertility

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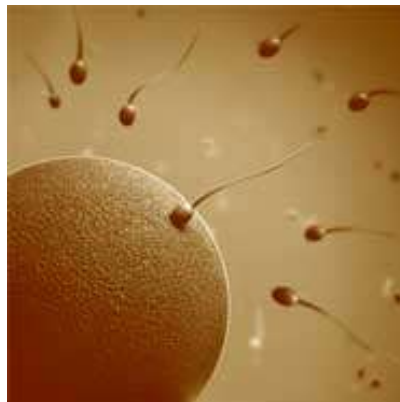


Environmental insults on Fertility

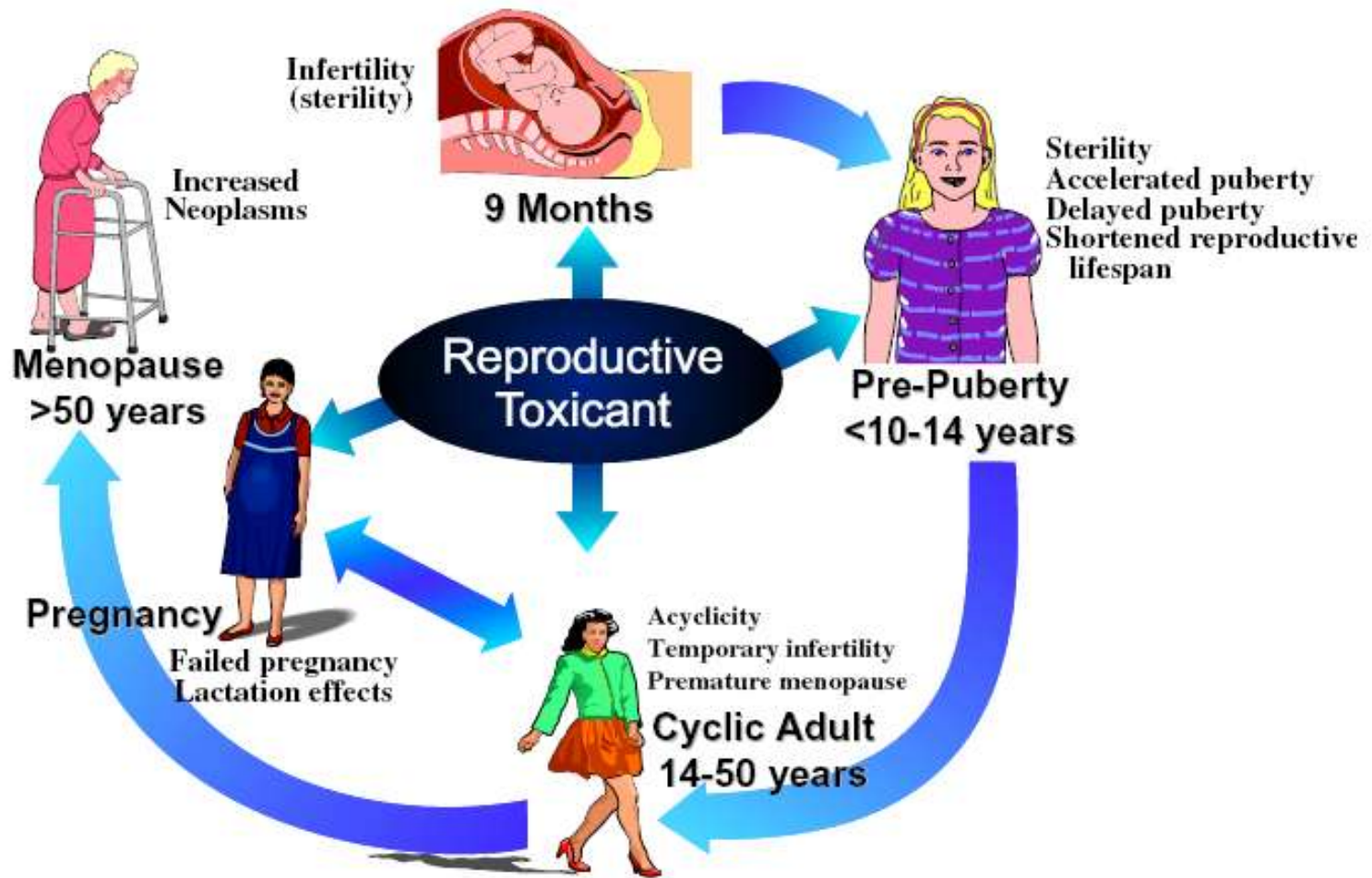
Chemical compounds and environmental pollutants have been shown to mimic or antagonize the effects of steroid hormones like estrogens and androgens. “Endocrine Disruptors”

These hormones are critical for normal male and female reproduction.

Successful Human reproduction relies on a competent sperm and oocyte to create an embryo capable of becoming a fetus.



Environmental Toxicants and Female Fertility



Cigarette Smoking and Infertility

Despite well known health hazards of smoking it is still prevalent in society.

More women smoking and starting at a younger age
(1/3 of teenage girls reported smoking).

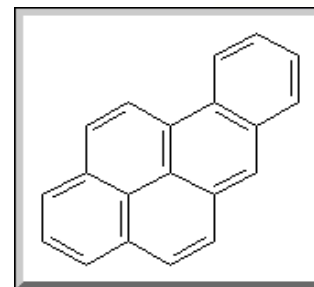
Coupled with trend towards delayed childbearing results in a greater incidence of clinical infertility.

(> 1 yr unprotected intercourse)

Benzo-[a]-pyrene (B[a]P)

- Many of the 4000 chemicals found in cigarette smoke have been shown to be toxic to the mammalian ovary.

- B[a]P is a member of the polycyclic aromatic hydrocarbons, resulting from incomplete combustion of fossil fuels.



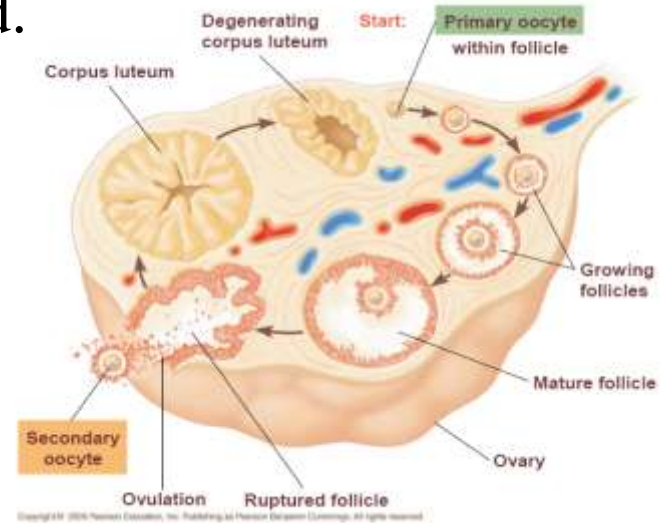
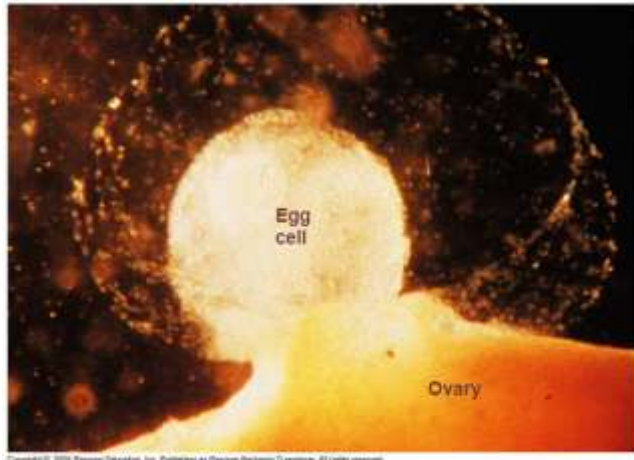
Benzo-[a]-pyrene



- B[a]P-induced follicle loss has been demonstrated in rats.
- Toxic actions of B[a]P is thought to be mediated through the Aryl Hydrocarbon Receptor (AhR).

Oocytes directly exposed to toxicants

Growing oocyte is bathed in follicular fluid.



Many toxicants have been identified in follicular fluid including:

pesticides and metabolites

cadmium

cotinine (metabolite of nicotine)

bisphenol A (BPA)

benzo-[a]-pyrene (B[a]P) Neal et al., Reproductive Toxicology, 2008

Aryl hydrocarbon receptor (AhR)

Plays a functional role in cellular proliferation and differentiation in developing vertebrates

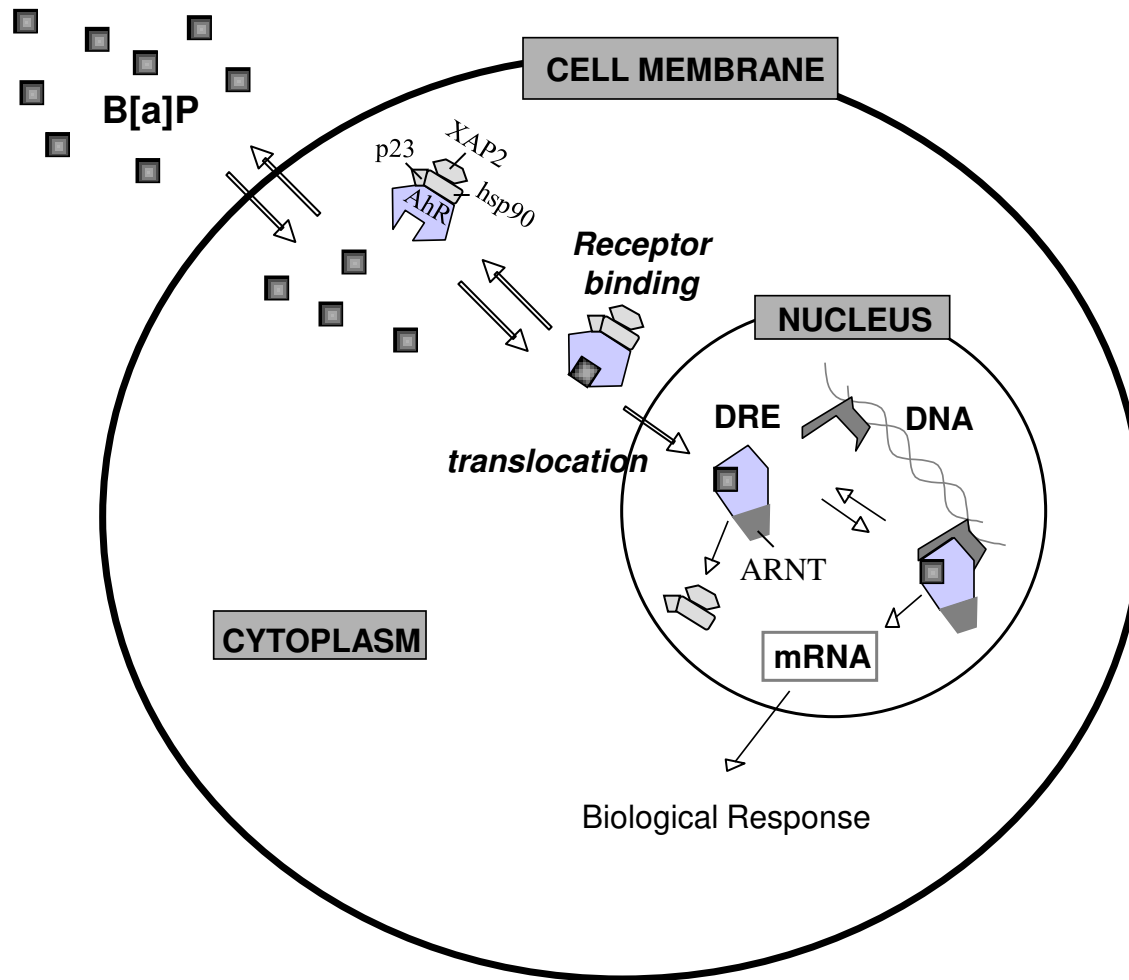
Adaptive Response

Vertebrates presumably evolved to use AhR as a way to bind and facilitate biotransformation and elimination of toxicants.

(TCDD exposure is the classical example)

Associated with toxicity is an alteration in gene expression leading to altered cellular processes and function.

AhR action in response to B[a]P



AhR antagonists

Resveratrol – phytoalexin found in the skin of grapes and is a constituent of red wine.

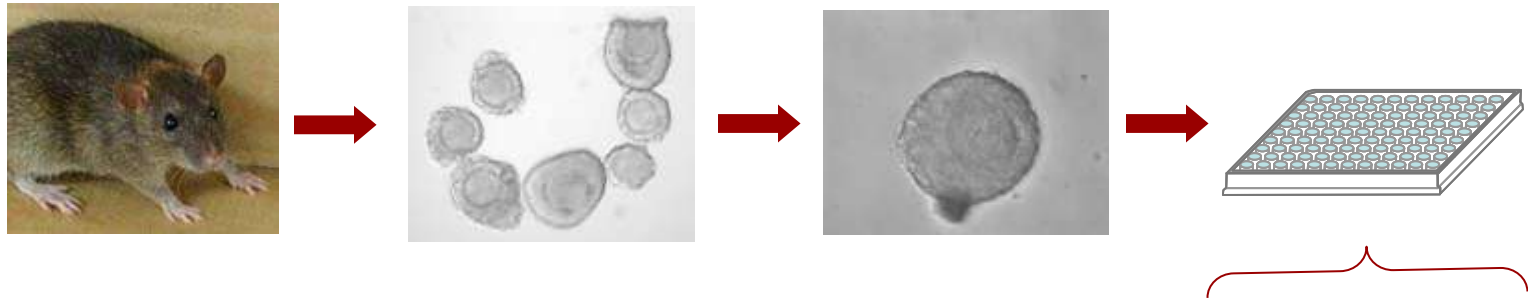
The amount of fermentation time that wine spends in contact with the grape skins is a determinant of resveratrol content. (higher in red wines – range 0.2 – 5.8 mg/L)

3', 4'- Dimethoxyflavone – pure AhR antagonist

Hypothesis

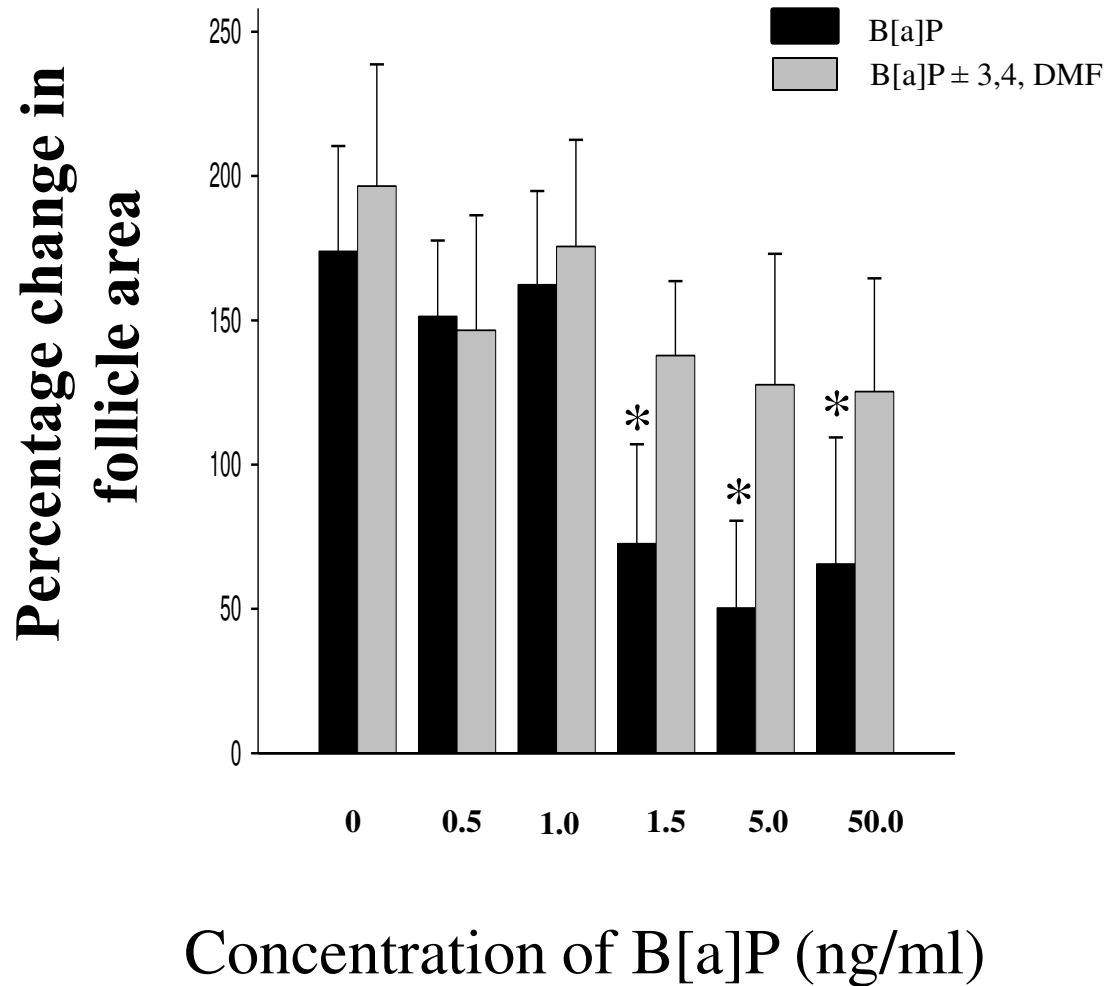
The deleterious effect of benzo-[a]-pyrene (B[a]P) will be attenuated by co-treatment with an aryl hydrocarbon receptor (AhR) antagonist

Methods



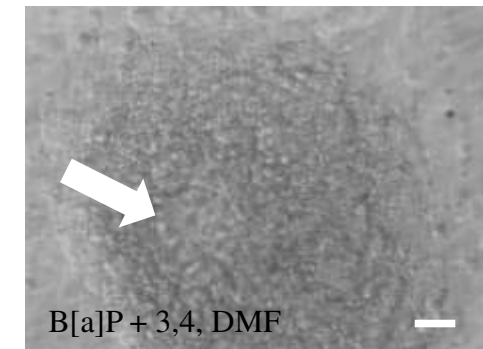
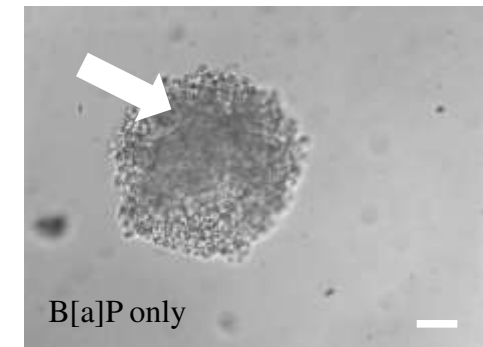
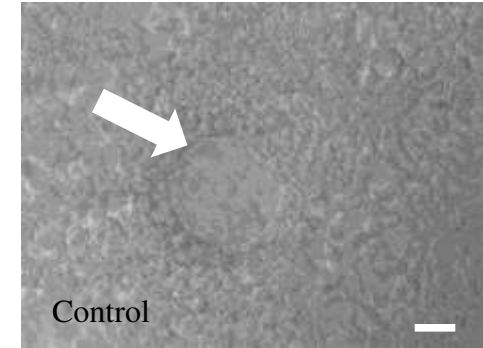
FCM ± B[a]P ± AhR antagonist

B[a]P ± AhR antagonist (3, 4, DMF)

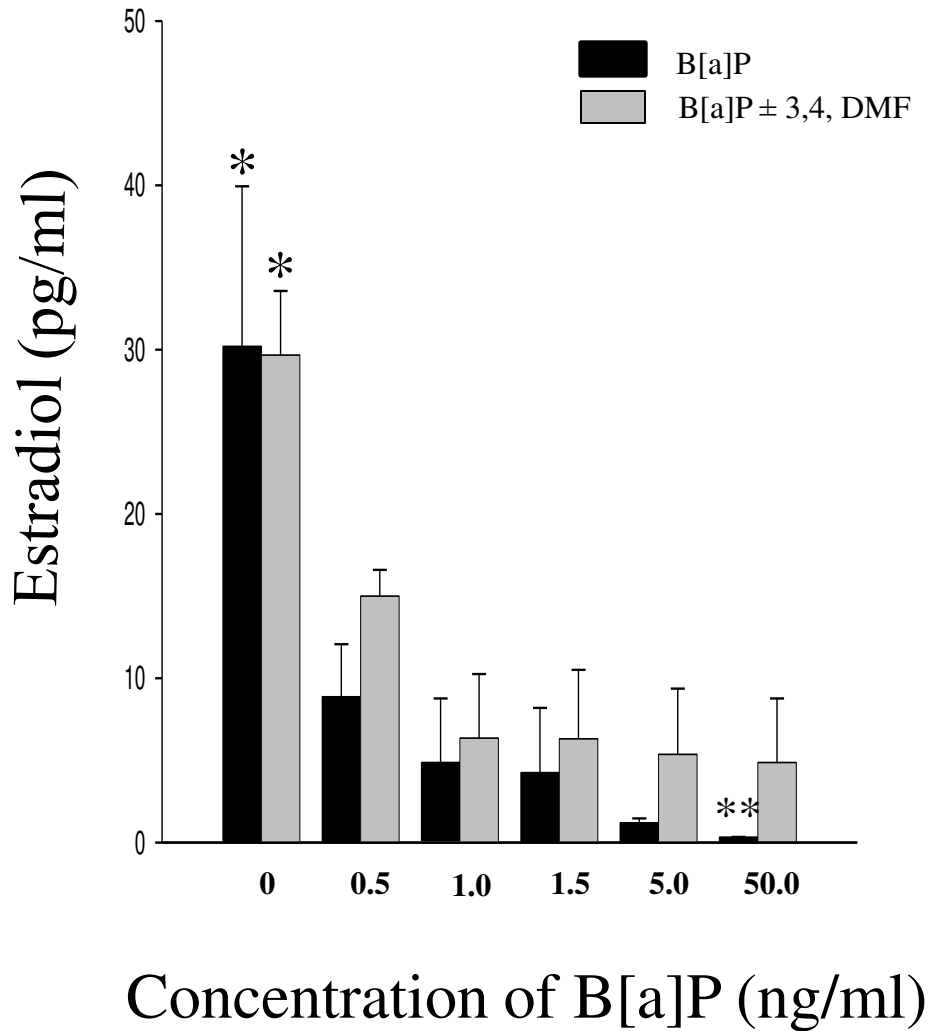


* P < 0.05

Representative Follicle Images



Estradiol output (spent media)



* $p < 0.05$

** $p < 0.01$

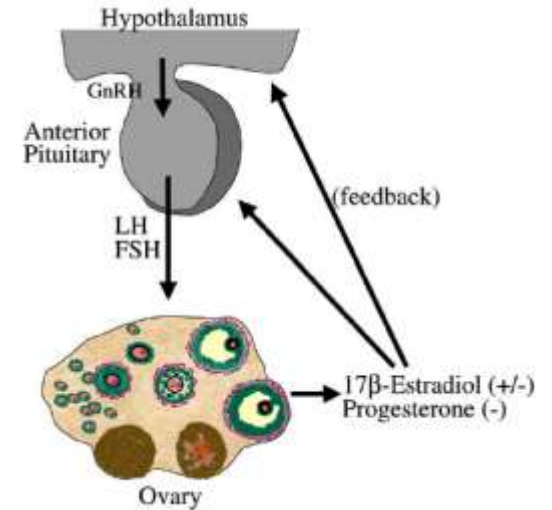
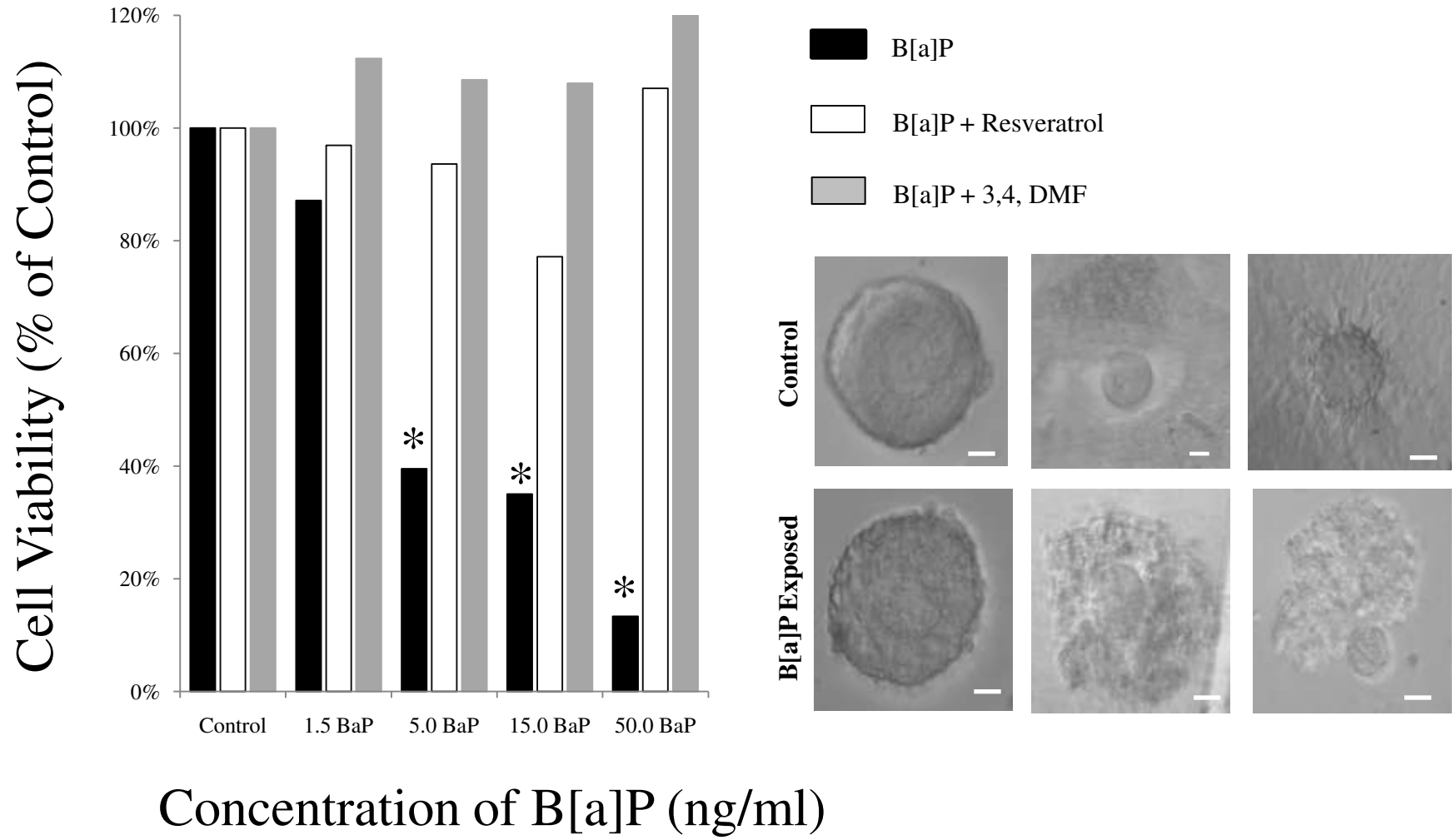


Figure Source: Hoyer et al.,
Cell Tissue Res 2005 Oct 322(1):99-106.

Cell Viability – MTS Cell Proliferation Assay



* p < 0.05

Mechanism(s) of B[a]P induced ovotoxicity

B[a]P and can be quantified in serum and follicular fluid;

- **Significantly higher levels in smokers;**
- **Significantly higher in women who did not conceive with IVF**

B[a]P attenuates follicular growth in an *in vitro* follicle culture system;

- **Estradiol production was lower in the B[a]P treated follicles;**
- **pre-antral follicle formation retarded in presence of B[a]P**

Effect of B[a]P is ameliorated by AhR antagonists

Mechanism(s) of B[a]P induced ovotoxicity

Impaired follicle growth:

- a) delayed oocyte maturation, and impaired ovulation.
- b) immature and/or incompetent (nuclear and cytoplasmic) oocyte ovulated due to incompetent GCs.
- c) delayed and/or improper timing of fertilization to coordinate proper pre-implantation embryo development with the implantation window resulting in greater TTP.

Toxicant induced follicular atresia:

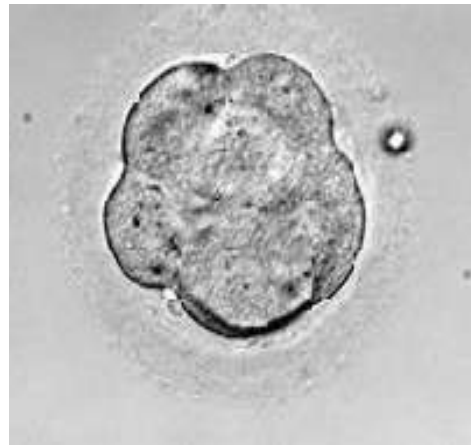
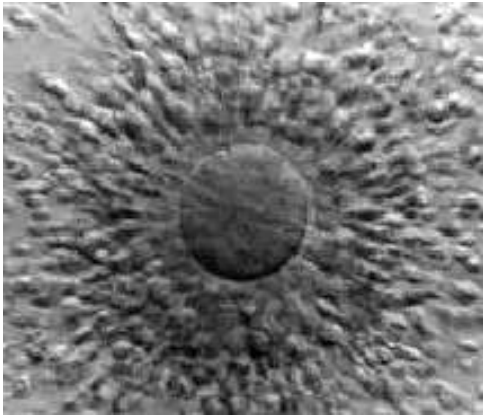
- a) reduces the follicle pool.
- b) premature ovarian failure, early onset of menopause.

Mechanism(s) of B[a]P induced ovotoxicity

Disruption of COC:

- Cumulus expansion disrupted.
 - Hormone influence altered.
 - Oocyte metabolism interrupted.
 - Nuclear and cytoplasmic competence compromised.
- May become fertilized and undergo pre-implantation development, but, implantation potential is questionable resulting in longer TTP or lower success observed using ART.

Discussion



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