Even through BPA is a weak oestrogen, there is a mechanism by which low levels of BPA could have a powerful health effect

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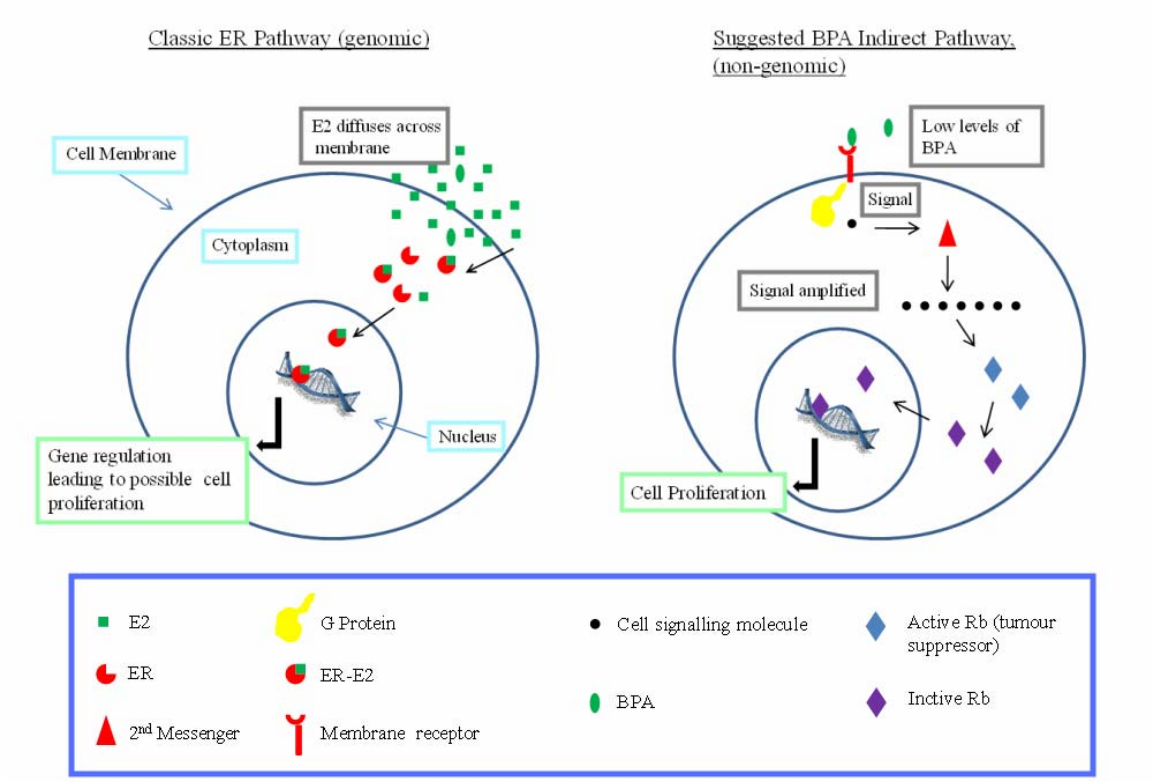

Diagram showing how BPA can indirectly influence cell proliferation.

A new study [EHP 117:1053–1058 (2009); Bouskine et al.] has shed some light on how bisphenol-A (BPA) can substantially interfere with hormone signalling within the body, even though it is a relatively weak xenoestrogen.

As regular readers of H&E will know, BPA is an increasingly controversial chemical additive commonly used in plastics such as food packaging and medical devices.

Concerns centre on its ability to mimic the hormone oestrogen, but sceptics of the potential for BPA to harm health argue that it is too weak a hormone to have an effect on cell function.

Here, we sketch out a mechanism by which BPA could have a much stronger effect than the sceptics argue, via an indirect pathway rather than a direct effect on the part of the cell nucleus which responds to oestrogen.

Note: We have tried to make this article as accessible as possible; if you are familiar with the cellular processes described, please be patient with our slightly long-winded explanation. Full references are at the bottom of this post.

KEY
ED = Endocrine Disruptor
ER = Oestrogen Receptor
E2 = Oestrogen

Is there a mechanism by which BPA, even though a weak xenoestrogen, can disrupt hormone signalling at environmentally-relevant concentrations?

Summary: The xenoestrogen BPA can stimulate cell proliferation and endocrine disruption at extremely low levels by acting on a G Protein Coupled Receptor. BPA does not therefore need to be present at the high levels needed for it to affect the nuclear Oestrogen Receptor (ER) in order to have a substantial effect.

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One of the main arguments against the idea that endocrine disruptors (EDs) such as BPA can have adverse health effects at low levels, is the "oestrogenicity" of such EDs at environmentally relevant levels is too weak to have an effect.

The argument is based on how EDs like BPA interact with the Oestrogen Receptor (ER-alpha or beta), found in the cell nucleus.

When ER is bound to oestrogen (E2), ER-E2 acts as a transcription factor, which "regulates" gene expression: the E2-ER complex binds to the DNA and regulates gene activity.

This may increase cell proliferation, especially during developmental periods, fetal, puberty, menses etc. This is a genomic effect.

Editor's note: The fact that BPA *may* increase proliferation is important to later understand why diethylstilbestrol (a highly problematic drug given to women between 1940 and 1980 to prevent miscarriage, and structurally similar to BPA) has a suppressive effect. We will return to this topic in a later post.

To get ER-mediated responses (genomic) with BPA or other EDs, very high concentrations are usually needed because they have a weaker affinity for the receptor. Sceptics often jump on this fact to say that BPA is not around at levels high enough to act directly on the ER and cause disruption.

The significance of the Bouskine study is that it shows a way in which BPA can act indirectly of the classic ER and exert effects at low doses, through a non-genomic rather than genomic pathway.

This is because of the way signalling works within cells: cells have receptors on their membranes, a bit like an antenna, which receive low level signals from, for example, hormones, drugs and xenochemicals.

The membrane receptors then transmit this signal elsewhere within the cell. One such membrane protein is a G protein. The signal is passed on from the G protein via what is known as a 2nd messenger.

The role of the 2nd messenger is to amplify the signal to make it much more effective. Thus an initial low-level signal will turn into a much stronger signal at the target.

The G protein in this study is called a G-protein coupled oestrogen receptor and can be activated by both oestrogen and BPA at picomolar (parts per trillion) or nanomolar (parts per billion) levels, which in turn activates transcription factors via 2nd messengers (which is non-genomic).

In this case the BPA mediates (via G protein and 2nd messengers) a chemical activation of two transcription factors, one called CREB and one called Rb. Rb is a cell cycle regulator, which helps govern cell division. Interference with this process, especially during critical windows of development, could have a range of permanent health effects [see H&E issue 13, PDF].

Thus we have a process in which low levels of BPA can cause endocrine disruption and possible adverse effects despite its low oestrogenicity, because only pico (10^12 M) or nanomolar (10^9 M) levels, are needed to elicit a response via the G protein coupled receptor mechanism.

These are the sorts of concentrations found in people's blood, and far lower than the BPA levels needed for a genomic ER response, which are around micromolar (10-6 M) levelsand 1,000 to 1,000,000 times higher.

Can other weak xenoestrogens have a similar effect?

Other EDs have been shown to act indirectly too. In one of my studies [Newby and Howard, 2005], I describe a mechanism whereby weakly oestrogenic PCBs can interfere with the action of an enzyme (SULTE 1E1) which breaks down and aids excretion of oestrogen and therefore regulates the amount of oestrogen that is bioavailable in the body [Kester et al., 2000; Kester et al., 2002].

In this case, if PCBs bind to the enzyme then more oestrogen is bioavailable to oestrogen sensitive tissues such as the testes/ mammary glands, and could cross the placenta resulting in increased oestrogen in the fetal bloodstream. This provides a mechanism where PCBs, although very weak oestrogens, could act to disrupt the endocrine system indirectly.

References

Bouskine A, Nebout M, Brücker-Davis F, Benahmed M, Fenichel P. (2009) *Low Doses of Bisphenol A Promote Human Seminoma Cell Proliferation by Activating PKA and PKG via a Membrane G-Protein–Coupled Estrogen Receptor*. Environmental Health Perspectives Volume 117(7): 1053-1058. [Link]

Newby J A and Howard C V (2006) *Environmental influences in cancer aetiology*. JNEM (15) 56-114. [Link]

Kester HA, Bulduk S, Tibboel D, et al., (2000) *Potent inhibition of Oestrogen Sulphotransferase by Hydroxylated PCB metabolites: A novel pathway explaining the oestrogenic activity of PCBs*. Endocrinology. 141: 1897-1900.

Kester HA, Bulduk S, van-Toor H, et al., (2002) *Potent Inhibition of Estrogen Sulfotransferase by Hydroxylated Metabolites of Polyhalogenated Aromatic Hydrocarbons Reveals Alternative Mechanism for Estrogenic Activity of Endocrine Disrupters*. J Clin Endocrinol Metabol. 87: 1142-1150.