The first endocrine-disrupting chemical inhibiting a coactivator peptide's binding

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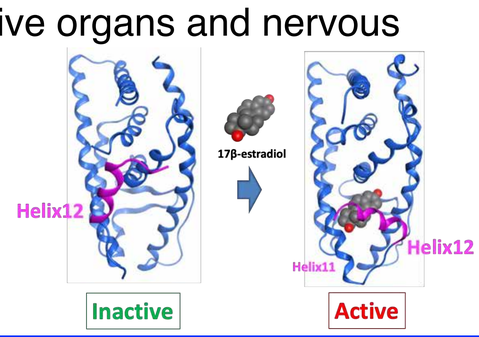
Bisphenol A (BPA) is a chemical that has gained significant attention due to its well-known endocrine-disrupting properties. As a result, BPA has been replaced with its derivatives, next-generation BPAs, which prioritize environmental and human safety. However, the safety of these next-generation BPAs is not fully evaluated. We have assumed that bisphenol's chemical structure is a privileged structure for nuclear receptors; therefore, we have screened a library of ca. 200 bisphenol derivatives for ERα and ERβ. We found that many next-generation BPAs, including BPAF and BPC, acted as antagonists for ERβ, despite being agonists for ERα. We confirmed that these chemicals act as coactivator-binding inhibitors for ERβ by surface plasmon resonance analysis using a coactivator peptide.

Background

BPA has garnered widespread attention as one of the most well-known EDCs. BPA induces adverse effects on experimental animals, even at low doses, especially on their reproductive organs and nervous systems. However, the molecular mechanisms of these BPA's low-dose effects are still yet clarified. These circumstances have facilitated replacing BPA with its derivatives, next-generation BPAs aiming at environmental and human safety.

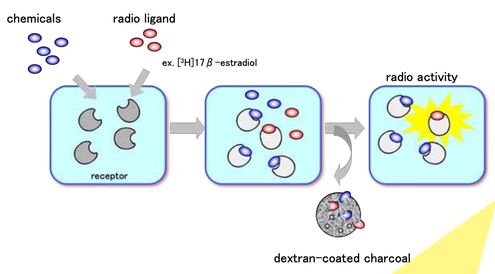


BPA binds to both estrogen receptor α (ERα) and ERβ, although its binding ability is much weaker than that of natural female hormone, 17β-estradiol.

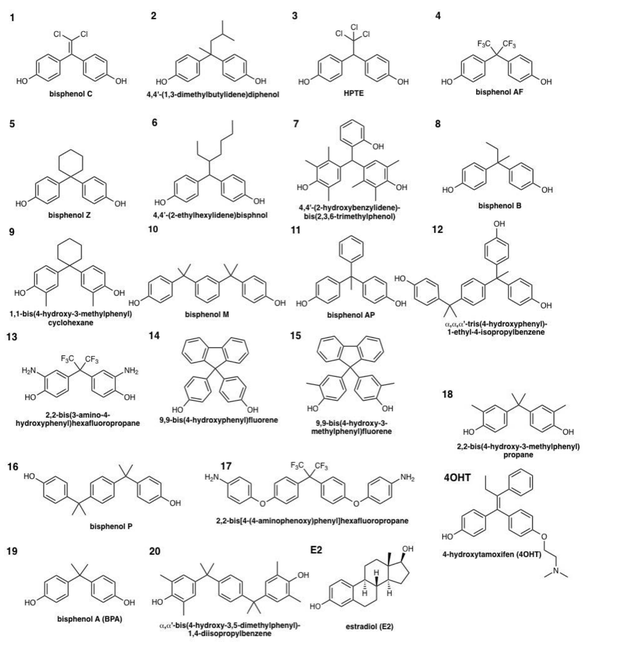
We have assumed that bisphenol's chemical structure is a privileged structure for nuclear receptors; therefore, we have screened a library of ca. 200 bisphenol derivatives for ERs.

Experimental & Results

① Competitive radio-ligand binding assay



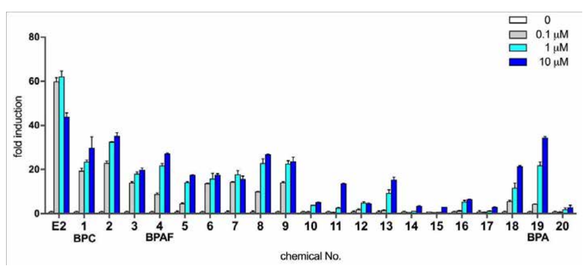
ca. 20 next-generation BPAs bind to ERα and ERβ stronger than BPA.



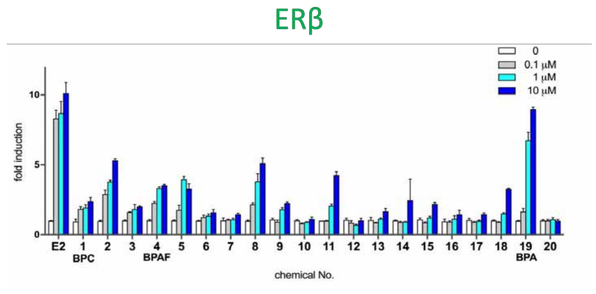
② Reporter gene assay

Agonist activity evaluated by reporter gene assay

ERα

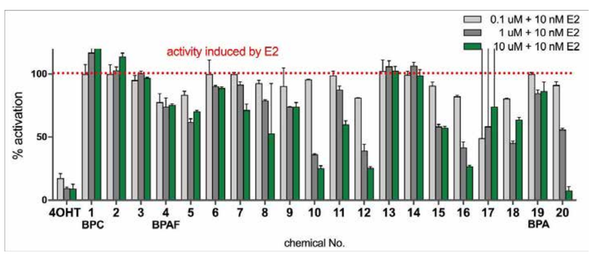


ERβ

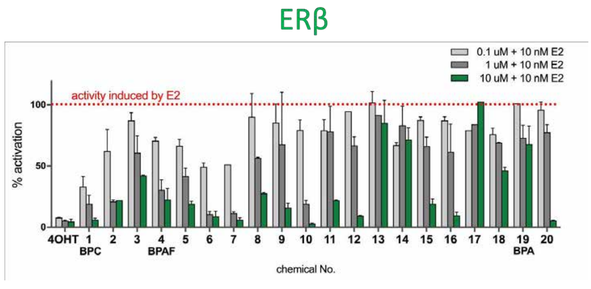


Antagonist activity evaluated by reporter gene assay

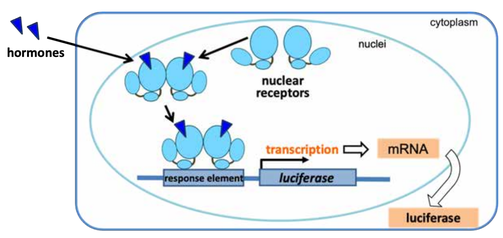
ERα



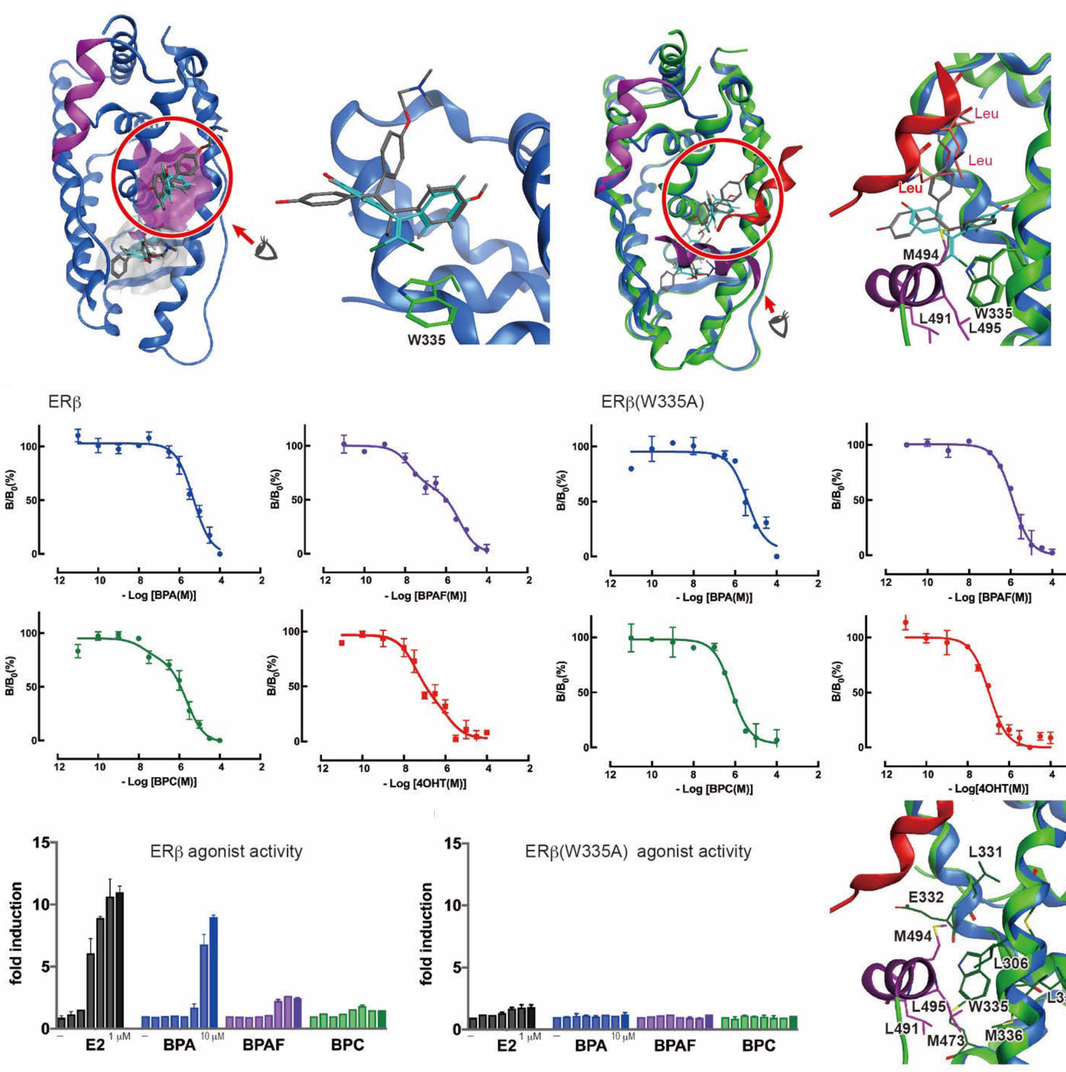
ERβ



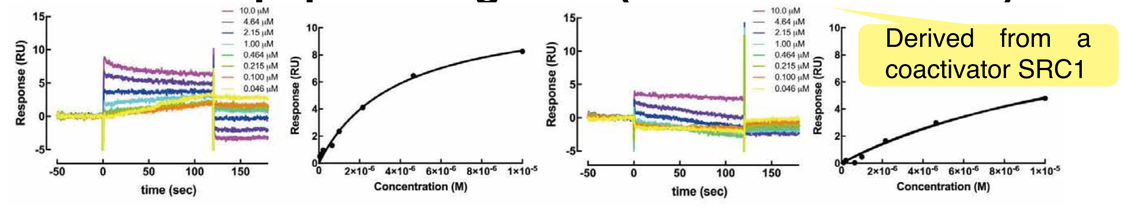
- Tri-cyclic bisphenols (ex. BPM) act as antagonists both for ERα and ERβ .
- Next-generation BPAs that strongly bind both to ERα and ERβ are ERα-agonists and ERβ-antagonists.



③ Docking simulation & binding ability of ERβ(W335A)



④ Surface plasmon resonance analysis using a coactivator peptide fragment (ERHKILHRLLQEG)



Conclusion

- ✓ Bisphenol AF (BPAF) and bisphenol C (BPC) bind to ERα much more strongly than does BPA itself.
- ✓ Tricyclic bisphenols, which have three benzene rings, are antagonists for ERβ, as they are as well for ERα.
- ✓ Many next-generation BPAs, including BPAF and BPC, acted as antagonists for ERβ despite being agonists for ERα.
- ✓ Next-generation BPAs act as coactivator-binding inhibitors for ERβ by surface plasmon resonance analysis using a coactivator peptide.

Iwamoto, M. et al. Bisphenol a derivatives act as novel coactivator-binding inhibitors for estrogen receptor β. *Journal of Biological Chemistry* **297**, 101173 (2021).