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THE TRANSACTIVATION ACTIVITY OF COMMON POLYPHENOLS ON BOTH RAT AND HUMAN ARYL HYDROCARBON RECEPTORS (AHR) IN THE PRESENCE AND ABSENCE OF AHR ENDOGENOUS (FICZ) AND XENOBIOTIC (TCDD) LIGANDS

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Introduction. Aryl hydrocarbon receptor (AhR) is known as a mediator of the response to xenobiotic. Recently, however FICZ (6-formylindolo[3,2-b] carbazole), a tryptophan (Trp) derivative, emerged as an endogenous ligand displaying the highest affinity to AhR. Several dietary polyphenols derived from plants can also activate AhR, suggesting that AhR may play important biological functions in normal life, which are little known. This study aims to examine the effect of common polyphenols and a mixture thereof on the transactivation activity of both human and rat AhR *in vitro* in the presence and absence of endogenous (FICZ) and xenobiotic (TCDD) AhR ligands. **Materials and methods.** The DR-CALUX® (Dioxin Responsive-Chemical Activated Luciferase gene eXpression) using rat DR-H4IIE and human DR-Hep G2 hepatoma cells were used to study AhR transactivation of seven common polyphenols, namely daidzein, quercetin, resveratrol, genistein, baicalin, curcumin, and chrysin and their mixture containing each compound at recommended doses available in the food supplements. **Results.** All of the polyphenols (excepted curcumin and chrysin for rat AhR and curcumin for human AhR) and their mixture activated AhR only in culture medium with Trp. The efficiency and EC_{50} were roughly similar in both cell lines, with a maximum efficiency of the mixture being 19.7 ± 0.5% and 24.4 ± 2.5% of the maximum FICZ response in rat and human cells, respectively. Interestingly, these agonistic activities were abolished when using the medium without Trp, except a weak effect for resveratrol. Hence, Trp was required for AhR activation of the active polyphenols and their mixture. DR-H4IIE cells were also exposed to polyphenols in the presence of TCDD/FICZ at EC_{50} and at excess concentrations TCDD (20 nM)/FICZ (1 µM), to study the possible antagonistic activity of the polyphenols towards these ligands. It appeared that daidzein, quercetin, genistein, and the mixture induced a higher AhR transactivity when co-exposed with FICZ EC_{50} than with TCDD EC_{50}. Daidzein and genistein exerted a synergistic effect in presence of both FICZ or TCDD (EC_{50} or excessive concentrations), while only FICZ EC_{50} allowed a higher response when co-exposed with quercetin and resveratrol (and baicalin, to a lesser extent), but a synergistic effect when co-exposed with the mixture. Curcumin indirectly antagonized the AhR since it inhibited the AhR activity of TCDD and FICZ at both EC_{50} and excessive concentration in a very similar way. The effect of FICZ and polyphenol co-exposure on human AhR transactivity in DR-Hep G2 was examined in culture medium with or without Trp. The polyphenol mixture caused a strong antagonism in either the medium with or without Trp, inhibiting the cell's normal response to EC_{50} FICZ from 100% down to 0% in medium with Trp (IC_{50} = 2.3 ± 0.27 µM) or to 10% in medium without Trp (IC_{50} = 1.7 ± 0.18 µM). The antagonistic behaviour of the mixture was due to its antagonistic components (quercetin, curcumin and chrysin), which behaved similar to the mixture. Resveratrol and genistein exerted opposite effects, synergism with EC_{50} FICZ in culture medium with Trp and antagonism in culture medium without Trp. Daidzein displayed an agonistic effect in both culture media, while baicalin remained inactive in medium with Trp, but exerted antagonisms in medium without Trp. **Conclusions**. DR-H4IIE and DR-Hep G2 responses to polyphenols depend on the presence of Trp. In the rat hepatoma DR-H4IIE cells, only curcumin and chrysin behaved as antagonists, while the other polyphenols (daidzein, quercetin, resveratrol, genistein and baicalin) were agonistic including their mixture. In contrast, in human hepatoma DR-Hep G2, three of the seven polyphenols were AhR antagonists (quercetin, curcumin, and chrysin) as well as their mixture, inspite of containing three agonists (daidzein, resveratrol, and genistein).

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