

CHARACTERISTICS OF HEPATIC AND LYMPHOCYTE MONOOXYGENASES IN SOUTH VIETNAM'S PEOPLE WITH CHLOROPHENOXY HERBICIDES EXPOSURE.

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Abstract

Long term effects of dioxin-like compounds on human organisms have been studied. An estimation of methods for bioindication of these compounds in vivo and in vitro was performed.

Introduction

The present study investigates long term effects of dioxin-like compounds on human organisms. The populations of Bin Mi and Tan Mi villages, Shong Be province, South Vietnam are chosen as a model. The former villages had been subjected to treatment with Agent Orange during 1965-1973, but the latter had not. An estimation of reliable methods for bioindication of dioxin-like compounds as well as their effects is also considered.

Methods

Benzo(a)pyrene-hydroxylase (BPH) activity was measured as described by Atlas et al.(1). Assay of antiprene (AP) and its metabolites in human urine after treatment with AP (18 mg/kg) was performed by HPLC (2).

Results and Discussion

BPH of blood lymphocytes has been used as an marker enzyme because of the known phenomenon of enzyme induction by 2,3,7,8-TCDD and of prognostic significance of BPH inducibility index (II). The latter is the ratio of BPH activity induced by benz(a)anthracene to the basal activity of the enzyme in the blood lymphocytes culture. Besides that the metabolism of AP has been studied in both groups using a HPLC method. Although the substantial differences in activities and inducibility of BPH between Tan Mi and Bin Mi inhabitants fail to be found it seems to be interesting to reveal the internal correlation connections of "marker" reactions studied, exactly BPH in blood lymphocytes and liver AP metabolism in these persons.

pyrene (OHAP) production (Table 1, column 1). This is the first confirmation in humans of the principle that the same molecular forms of cytochrome P-450 are expressed in the different tissues. Up to now the suggestion of O. Pelkonen (University of Oulu, Finland) is known that the induction of cytochromes belonging to P-450I family is systemic in rodents but organospecific in humans. The latter assertion was a consequence of BPH induction reveal only in the placentas of smoking women, but not in lymphocytes (3). Data shown in Table 2, Column 1 do not confirm that suggestion. The presence of strong correlation between the BBPH in lymphocytes of Bin Mi inhabitants (subjected to Agent Orange) and the Activity of this cytochrome P-450 isoform catalyzing OHAP production in liver (4) testifies to a systemic although diverted character of the effects of agents inducing cytochrome P-450 IA1 (like residual quantities of 2,3,7,8-TCDD in the present instance). In the second, this correlation confirms our right choice of such non-invasive method of bioindication as AP metabolites detection. This method allows us to corroborate the data of "lymphocyte test" and, perhaps, can exchange the latter in future.

Table 1: Correlations among P-450-dependent and metabolic parameters in inhabitants of Tan Mi village. * P<0.05, ** P<0.01, *** P<0.001.

| | BBPH 1 | IBPH 2 | II 3 | absolute value | | | | ratio value | | | | |
|----------------|----------------------|--------------|--------------|----------------|--------------|--------------|--------------|--------------|--------------|--------------|--------------|--|
| | | | | HMA 4 | NORA 5 | OHAP 6 | AP 7 | HMA 8 | NORA 9 | OHAP 10 | AP 11 | |
| II | n-24 -0.18 | | | | | | | | | | | |
| absolute value | HMA n-9 -0.16 | n-7 -0.38 | n-7 0.05 | | | | | | | | | |
| | NORA n-6 -0.68 | n-4 0.98 | n-4 -0.10 | n-7 0.49 | | | | | | | | |
| | OHAP n-7 0.92 | n-5 0.89 | n-5 -0.01 | n-8 -0.05 | n-7 0.75 | | | | | | | |
| | AP n-8 0.02 | n-6 0.91 | n-6 -0.12 | n-7 0.16 | n-6 0.26 | n-7 0.22 | | | | | | |
| ratio value | HMA n-9 -0.22 | n-7 -0.70 | n-7 -0.19 | n-10 0.85 | n-7 -0.59 | n-8 -0.46 | n-9 -0.17 | | | | | |
| | NORA n-6 -0.12 | n-4 0.05 | n-4 -0.21 | n-7 0.56 | n-7 -0.04 | n-7 -0.31 | n-6 -0.47 | n-7 0.20 | | | | |
| | OHAP n-7 0.50 | n-5 0.67 | n-5 0.48 | n-8 -0.57 | n-7 0.85 | n-8 0.54 | n-7 -0.26 | n-8 -0.84 | n-7 -0.18 | | | |
| | AP n-8 -0.18 | n-6 0.23 | n-6 0.07 | n-9 -0.39 | n-6 -0.42 | n-7 -0.14 | n-9 0.11 | n-9 -0.21 | n-6 -0.59 | n-7 -0.44 | | |
| S Met. | n-9 0.30 | n-7 0.31 | n-7 0.05 | n-10 0.59 | n-7 0.78 | n-8 0.64 | n-9 0.66 | n-10 0.14 | n-7 -0.52 | n-8 0.19 | n-9 -0.42 | |

A negative correlation between low BBPH and II values in Bin Mi inhabitants should be noticed. The BBPH in these persons correlates as with a decrease of the relative level of unchanged AP yield as with a total increase of monooxygenative reactions in the liver. The latter is caused first of all by an increase of BPH-specific product OHAP (4).

The presence of correlations among induced BPH activity (IBPH) in lymphocytes and the metabolic characteristics of AP in the liver (where besides the specific product OHAP the strong correlation is visible also with norantiprene (NORA)) again sets on the agenda a question about the number of cytochrome P-450 isoform in human blood lymphocytes. Intercommunication between IBPH and the absolute value of NORA has been revealed also during analysis of the samples from Bin Mi village (Table 2, column 2). In this group the expressed correlations are available among the specific BPH-dependent metabolite OHAP, the value of AP unchanged and increase of NORA and 3-hydroxymethylantiprene (HMA) (Table 2, columns 4 and 5) which are specific for the other cytochrome P-450 forms. This unusual fact can be explained proceeding from the recent data of Davies and Safe (5) that polychlorinated biphenyls falling under so-called "PB-type" effectively decrease the immunosuppressive effects of 2,3,7,8-TCDD. This inhibition testifies in the first that the mechanism of 2,3,7,8-TCDD action can not be restricted only by "receptor" route (via Ah receptor) as PB-type inducers do not act via that receptor protein. In the second it can be suggested that besides immunosuppression dioxin using non-receptor route can activate in the liver the other cytochrome P-450 forms apart P-450 IA1.

Table 2: Correlations among P-450-dependent and metabolic parameters in inhabitants of Bin Mi village. * P<0.05, ** P<0.01, *** P<0.001.

| | BBPH 1 | IBPH 2 | II 3 | absolute value | | | | ratio value | | | | |
|----------------|--------------------|--------------------|--------------------|---------------------|---------------------|---------------------|----------------------|--------------------|---------------------|--------------------|----------------------|--|
| | | | | HMA 4 | NORA 5 | OHAP 6 | AP 7 | HMA 8 | NORA 9 | OHAP 10 | AP 11 | |
| II | n-42 * -0.34 | | | | | | | | | | | |
| absolute value | HMA | n-21 0.23 | n-22 0.22 | n-20 -0.14 | | | | | | | | |
| | NORA | n-16 0.14 | n-17 * -0.49 | n-15 -0.42 | n-26 0.35 | | | | | | | |
| | OHAP | n-18 * 0.54 | n-19 -0.21 | n-17 -0.33 | n-30 ** 0.51 | n-25 *** 0.80 | | | | | | |
| | AP | n-21 0.02 | n-22 0.25 | n-20 0.29 | n-33 0.39 | n-27 ** 0.51 | n-30 0.20 | | | | | |
| ratio value | HMA | n-18 -0.28 | n-19 0.34 | n-17 0.04 | n-31 0.32 | n-24 -0.32 | n-29 -0.28 | n-31 -0.30 | | | | |
| | NORA | n-13 0.47 | n-14 -0.39 | n-12 -0.31 | n-24 -0.01 | n-24 0.82 | n-24 ** 0.51 | n-24 0.15 | n-24 -0.38 | | | |
| | OHAP | n-16 0.26 | n-17 -0.02 | n-15 * -0.54 | n-29 0.03 | n-24 0.23 | n-29 *** 0.58 | n-29 * -0.44 | n-29 ** -0.37 | n-24 0.09 | | |
| | AP | n-18 * -0.45 | n-19 -0.27 | n-17 ** 0.60 | n-31 ** -0.46 | n-24 -0.52 | n-29 *** -0.62 | n-31 ** 0.25 | n-31 0.15 | n-24 * -0.48 | n-19 *** -0.79 | |
| S Met. | n-18 * 0.60 | n-19 -0.08 | n-17 -0.23 | n-31 *** 0.64 | n-24 0.84 | n-29 *** 0.94 | n-31 ** 0.46 | n-31 -0.33 | n-24 0.54 | n-29 0.34 | n-31 ** -0.54 | |

That finds its reflection in the correlation of the production of all known AP metabolites in the liver of inhabitants of Bin Mi village that had been exposed to dioxin.

In connection with the foregoing it seems not surprising that the strong correlation exists among absolute and relative yield values of OHAP, NORA, HMA, unchanged AP and the total production of all metabolites (S Met.) of this "marker" xenobiotic in the livers of the people in control group (Table 1) and particularly in exposed group (Table 2).

Considering the internal communications of studied parameters of BPH in lymphocytes and AP metabolism in liver of inhabitants of Tan Mi and Bin Mi villages one can estimate a degree of similarity or difference between the populations of compared villages. As a preliminary a weak inter-communication can be marked among the studied parameters in the population of Tan Mi village (not subjected to the action of dioxin-like compounds). That is most likely caused by a high genetic heterogeneity of that population. The appearance of correlation connections among those parameters in Bin Mi population is caused likely by smoothing of genetic differences by the direct inducing effect of residual contents of dioxin-like compounds in the organism of the South Vietnam inhabitants.

From our point of view the further studies on bioindication of distant results of dioxin effects in some regions of South Vietnam apart foregoing approaches can develop with inculcation of immunochemical methods of quantitative indication of marker cytochrome P-450 IA1 in placentas of women in compared regions.

References

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