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ORGAN SPECIFICITY OF ARYL HYDROCARBON HYDROXYLASE INDUCTION BY CIGARETTE SMOKE IN RATS AND MICE.

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The influence of cigarette smoke in the appearance of certain types of cancer, notably in the respiratory tract, is well known. Specific fractions of cigarette smoke condensates appear to present a significant mutagenic activity [1]. Cigarette smoke inhalation has also been demonstrated to induce the activity of aryl hydrocarbon hydroxylase (AHH) in the lungs of animals [2,3] as well as in the pulmonary alveolar macrophages and the placentas of human smokers [4,5,6]. This consideration acquires considerable importance when one considers (a) that the cytotoxicity of polycyclic hydrocarbons (with which are generally associated the carcinogenic potentials of cigarette smoke) augments with an increase of AHH activity [7] and (b) that a correlation exists between the induction of AHH and the appearance of certain types of cancer [8].

The aim of the present study was to investigate further the mechanism of cigarette smoke induction of AHH activity in different tissues. Male Sprague-Dawley rats and male C3H/Ico, C57Bl/6J, DBA/2J and AKR/Rho Ico mice were allowed to inhale cigarette smoke during periods of fifteen minutes, in a type II Hamburg inhalation apparatus (Heinz Borgwaldt, Hamburg 50, Germany). In all cases, the smoke leaving the cigarettes was diluted by 15 (rats) or 30 (mice) volumes of air before being introduced into the inhalation chamber. When several inhalations were performed, they were administered at 2 hour intervals. The animals were always sacrificed 4 hours after the last inhalation. The AHH activity was measured in the livers, the lungs and the kidneys. The conditions were described elsewhere [9] for the liver and the lung, the kidney enzymatic activities were determined in the same manner as indicated for the lung.

Fifteen minutes of smoke inhalation produces a significant AHH induction in the lung and the kidney in the rat. This induction is very rapid and peaks already 4 hours after the initial smoke inhalation [10]. If successive inhalations are administered to the rats, two phenomena are observed : (i) up to four inhalations, each treatment induces further the AHH activity; there is in fact, a clearcut additive effect of the first two inhalations. (ii) After the fourth inhalation, the subsequent treatments do not cause an augmentation of AHH activity. On the contrary, the enzymatic activity decreases slowly after the sixth inhalation in the lung and after the fourth in the kidney. This observation might be explained in several ways : accelerated metabolism

of the inducing agent(s) by the induced enzymes, toxic effect of cigarette smoke component(s), feedback control at the cellular level...

The AHH activity was also determined in the tissues of mice which were submitted to three successive treatments. Under these experimental conditions, the cigarette smoke induced very significantly the AHH activity in the lungs of all the strains studied, while it did not affect the enzymatic activity in the livers of the same animals. The kidney AHH activity was significantly induced in two strains of mice (C57Bl/6J and C3H/Ico) but was not modified in the other two strains (AKR/Rho Ico and DBA/2J).

AHH activity in lung, kidney and liver of control and cigarette smoke treated rats and mice.

Species	Strain	Number of Inhalations	AHH Activity		
			Lung	Kidney	Liver
Rat	Sprague-Dawley	none	50±7	58±24	10.3±1.1
		1	172±53*	303±70*	9.7±1.2
		2	299±38*	553±83*	10.8±1.0
		4	389±73*	811±131*	8.5±2.3
		6	420±52*	757±156*	10.5±1.4
		8	333±79*	661±219*	9.6±1.6
Mice	AKR/Rho Ico	none	69±19	17±5	8.26±2.41
	AKR/Rho Ico	3	203±78*	19±3	7.69±4.71
	DBA/2J	none	52±12	14±9	1.47+0.36
	DBA/2J	3	183±64*	17±4	1.47±0.26
	C57Bl/6J	none	154±83	17±2	2.58±0.50
	C57Bl/6J	3	307±47*	32±6*	3.24±0.49
	C3H/Ico	none	71±31	16±8	3.30±0.41
	C3H/Ico	3	224±111*	41±10*	3.58±0.59

Enzymatic activities (Means + Standard Deviation) are expressed in pmol/h x mg proteins in the lung and in the kidney, and in nmol/h x mg proteins in the liver. Each group contains 6 animals.

* $P < 0.01$ when compared to the corresponding non-treated group.

The intraperitoneal administration of polycyclic hydrocarbons induces rapidly the AHH activity in the tissues of certain strains of mice, like the C57Bl/6J and the C3H/Ico. In other strains of mice (AKR/Rho Ico, DBA/2J), the enzyme is not affected by the inducing agent [11,12,13]. Nevertheless, it was more recently described that the administration of 2,3,7,8-tetrachlorodibenzo-p-dioxin, an inducer belonging to the same group as the polycyclic hydrocarbons, induced very significantly the AHH activity in the various tissues of mice belonging to a previously called non-inducible strain [14]. This last observation led to the hypothesis of the existence of a less efficient receptor site in the genetically non responsive strains [15].

In our study, we were able to demonstrate that an agent (to be identified) present in the cigarette smoke was able to induce the AHH activity in the lungs of rats and mice, the latter belonging to either an inducible or a non-inducible strain. This observation, confirming the work of Abramson and Hutton [3], could be explained either by a lung specific receptor or by the administration route of the responsible agent. We also discovered that,among other tissues studied, the enzymatic activity was not modified in the liver and in the bowel (results not shown), but was significantly induced in the kidneys. If one relates this observation to the fact that the kidney AHH activity was not induced in the non-inducible strains, one is prompted to postulate one or several of the following hypotheses : (1) the kidney receptor is more sensitive than the liver or bowel one; (2) the inducing agent reaches a higher concentration in the lung compared to the kidney and in the kidney compared to the other tissues; (3) the responsible inducers might not be the same in the lung as in the kidney.

In conclusion, our study demonstrates the great sensitivity to a common agent of our environment, of a lung enzyme which is implicated in the chemical carcinogenesis.

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