1. INTRODUCTION

Studies conducted so far have indicated that hormones acting as ligands of cytoplasmic and nuclear receptors (growth hormone, glucocorticosteroids, thyroid hormones) influence transcriptional level of genes encoding cytochrome P450 (CYP) isoenzymes [1-3]. All the above-mentioned hormones are controlled by the hypothalamo-pituitary axis. It is also known that the hypothalamus is closely innervated by serotonergic axons projecting from raphe nuclei (dorsal nuclei B6, B7 and median nuclei B, B5). Serotonergic neurons reach hypothalamic nuclei forming paracortical neurosecretory system (the paraventricular and arcuate nuclei). Thus, it can be assumed that brain serotonergic projections to the hypothalamic influence hepatic cytochrome P450 expression via the above-mentioned hormones.

The aim of our study was to investigate the effect of damage to the serotonergic system on the expression of liver cytochrome P450 and serum level of the key hormones (growth hormone, thyroid hormones and corticosterone) that contribute to this process.

2. MATERIALS AND METHODS

The experiments were carried out on male Wistar rats. The 5,7-DHT (5,7-dihydroxytryptamine), a specific serotonergic neurotoxin was injected into dorsal and median raphe nuclei (in a dose of 10 μg/raphe nucleus) or intracerebroventricularly (in a dose of 770μg/ventricle). Ten days after the neurotoxin injection, brain structures, liver tissue and blood were collected and prepared for further analysis. The levels of noradrenaline (NA), dopamine (DA) and serotonin (5-HT) in the brain structures were determined by a high pressure liquid chromatography (HPLC) with an electrochemical detection.

The activity of individual cytochrome P450 isoenzymes was determined in microsomal fraction of the liver, based on the velocity of reactions specific for individual isoenzymes: caffeine 3-N-demethylation (catalyzed by CYP2C11 and CYP1A) and caffeine 5-hydroxylation (catalyzed by CYP1A), testosterone hydroxylation at positions 2β, 6β (catalyzed by CYP1A); 2α, 16α (catalyzed by CYP3A11); 7α (catalyzed by CYP3A) and 16β-hydroxylation (catalyzed by CYP3A). Specific metabolites formed in vitro were assayed using HPLC with UV of fluorescence detection [4]. Serum concentrations of hormones and interleukins were estimated using ELISA kits.

3. RESULTS

4. Analysis

5. Results

CONCLUSIONS

1. Either mode of lesions (intracerebroventricular or intratuberalus) reduced the serotonin level in all the brain structures examined. In the hypothalamus, the 5,7-DHT level fell to 35% and 18% of the control value after injection to the raphe nuclei and lateral ventricles, respectively.

2. In the liver, similar effects were observed after either mode of lesion. 5,7-DHT increased the activity of CYP1A, CYP3A and CYP2C11, while the activity of CYP2A, 2B, 2C6 and 2D remained unchanged.

3. The results obtained indicate that brain serotonergic system contributes to the regulation of liver cytochrome P450. However, its effect on the main male isoforms (CYP2C11, CYP3A) is opposite to that observed for dopaminergic or noradrenergic systems.

REFERENCES


SUMMARY

5.7-DHT

Enzyme activity

Protein level

ACKNOWLEDGMENTS

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