Transcription in Nerve Cells and Hepatocytes of Rats with Different Narcologic Resistance in Early Postnatal Ontogenesis

V. N. Yarygin, E. V. Lipkina, A. G. Mustafin, Yu. G. Lipkin, and S. K. Sudakov

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The effects of morphine and the protease inhibitor antipain on the synthesis of RNA in nerve cells and hepatocytes of WAG and F344 rats aged 3 and 14 days were studied. Slices of the sensorimotor cortex, hypothalamic ventromedial nucleus, locus ceruleus, upper cervical sympathetic ganglion, and liver were incubated *in vitro* with the agents and the isotope. The control and experimental parameters of the level of transcription differed for the two rat strains and different age groups.

Key Words: *narcologic resistance; morphine; postnatal ontogenesis; transcription*

Study of the molecular mechanisms of morphine action, one of which consists in altering transcription, opens up new vistas in the treatment of narcomanias caused by morphinelike substances. Some reports speculate about a possible genetic predisposition for narcotics use and the formation of dependence and tolerance in human beings and animals [5].

This study was aimed at investigating the age-specific features of RNA synthesis in nerve cells and hepatocytes of F344 and WAG rats differing in narcologic resistance.

MATERIALS AND METHODS

Hepatocytes and neurons of the upper cervical sympathetic ganglion (UCSG), sensorimotor cortex (SMC), hypothalamic ventromedial nucleus (VMN), and locus ceruleus of 50 F344 and WAG rats aged 3 and 14 days were examined. Surviving slices were incubated routinely [2] with morphine, the protease inhibitor antipain (final concentrations in the incubation medium 8 and 0.08 mM, respectively), and ^{3}H-uridine. Control slices were incubated in medium without the agents. The results were expressed in specific radioactivity of slices (cpm/mg wet weight). The method for assessing the absolute and relative incorporation of the isotope in RNA molecules was described previously [2]. The data were statistically processed using Student's *t* test.

Department of Biology, Russian State Medical University, Moscow

RESULTS

The results confirm the alteration of transcription activity in the course of individual development [6]. A low level of transcription was observed in nerve cells of all examined structures of 3-day-old rats of both strains, except for the UCSG neurons (Tables 1 and 2). At the age of 14 days the parameters of transcription activity sharply increased, but not in the locus ceruleus or hepatocytes of WAG rats, the maximum being observed in the UCSG of F344 rats and the VMN of WAG rats. The control parameters of the two strains differed appreciably for the UCSG of 3-day-old rats and for the UCSG, locus ceruleus, and hepatocytes of 14-day-old rats. This may be proof of genotypic differences of animals with different levels of sensitivity to narcotics [5,10].

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TABLE 1. Variations of ^{3}H-Uridine Incorporation in Total RNA of Nerve Cells and Hepatocytes of WAG Rats under Conditions of Exposure to Morphine and Antipain, % of Control

Age, days	Series	UCSG	SMC	VMN	Locus ceruleus	Hepatocytes
3	Control	165.82±17.93	39.19±6.52	91.19±9.68	50.88±5.80	32.24±8.79
	Morphine	*	*	-49.44	*	*
	Antipain	-45.33	*	-55.67	*	*
	Morphine+antipain	*	*	*	*	*
14	Control	154.29±5.82	155.93±33.17	293.29±56.00	50.54±16.53	67.27±5.68
	Morphine	-29.02	+70.74	*	+129.5	*
	Antipain	*	+67.08	*	+282.5	*
	Morphine+antipain	-31.40	+114.8	*	+236.3	*

Note. Here and in Table 2: control parameters expressed in cpm/mg wet weight; rise (+) and fall (-) in comparison with the control. *Unreliable difference.

TABLE 2. Variations of ^{3}H-Uridine Incorporation in Total RNA of Nerve Cells and Hepatocytes of F344 Rats under Conditions of Exposure to Morphine and Antipain, % of Control

Age, days	Series	UCSG	SMC	VMN	Locus ceruleus	Hepatocytes
3	Control	160.72±7.45	43.53±6.33	47.53±8.27	52.15±2.29	50.61±12.79
	Morphine	-53.04	*	+131.8	*	*
	Antipain	-41.54	*	*	*	*
	Morphine+antipain	-40.19	-42.13	*	*	*
14	Control	241.70±9.13	217.49±26.54	238.59±52.24	123.33±8.91	163.82±21.37
	Morphine	-37.36	*	*	*	-52.43
	Antipain	*	*	*	*	-52.86
	Morphine+antipain	-70.08	*	*	+105.9	-49.87

According to our findings, the reaction of nerve cells to morphine changes with age in all the examined structures of WAG rats and in the VMN of F344 rats. Morphine exerted a potentiating effect on VMN neurons of 3-day-old F344 rats and on the SMC and locus ceruleus neurons of 14-day-old WAG rats. This may be explained by qualitative and quantitative changes in the transcribed DNA sites, specifically, of morphine-sensitive sites, in the course of ontogenesis [1,6]. The effect of antipain coincided with the effect of morphine on the neurons of SMC, VMN, and locus ceruleus of WAG rats of both age groups. In the same structures of F344 rats antipain did not reliably alter the isotope incorporation. Similar reactions of the UCSG were observed in rats of both strains.

For hepatocytes, the results were especially interesting. The reaction of the hepatocyte transcription apparatus did not differ from the control parameters for exposure to morphine, antipain, and a combination thereof in WAG rats of both age groups and for 3-day-old F344 rats. The agents suppressed the isotope incorporation in 14-day-old F344 rats. It is, however, difficult to draw a definite conclusion for this case.

The hypotheses about the existence of a protease mechanism of RNA synthesis in exposure to morphine [1] are confirmed for VMN neurons of 3-day-old rats of both strains; joint injection of the agents canceled the morphine effect and the baseline values were observed. In the UCSG of rats of both strains the combined effect of the agents was no different from the effect of morphine alone. The same was observed for SMC and locus ceruleus neurons of 3-day-old F344 rats and for SMC neurons of 14-day-old F344 rats.

The examined rat strains are characterized by genetic differences manifested in the metabolism of monoamines and endogenous opioids, as well as by differences at the level of the opiate and adrenoreceptors [5]. These differences determine the peculiarities in the realization of the mechanisms of narcotic effects. The morphine-induced alteration of the level of transcription in rats of different age groups may be attributed to continuing differentiation of certain elements of the studied structures in early ontogenesis, to specific features in the functioning of the genetic apparatus and in the metabolism of different classes of proteins in the nuclei and directly in the chromatin complex of the cells,

and to age-specific features of the transmitter systems [3,4,9].

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