EXPERIMENTAL BIOLOGY

Effects of Morphine and Antipaine on RNA Production in Neurons and Hepatocytes of WAG and F344 Rats

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Effects of morphine and of the protease inhibitor antipaine on RNA synthesis in nerve cells and hepatocytes of 1-, 6-, and 12-month WAG and F344 rats is studied. Slices of sensorimotor cortex, hypothalamic ventromedial nucleus, blue spot, superior cervical sympathetic ganglion, and liver were incubated with the drugs and ^{3}H-uridine *in vitro*. Control and experimental levels of transcription differed in examined structures and changed in the course of postnatal ontogenesis.

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

There is evidence that morphine affects the synthesis of RNA; proteases can be one of the mechanisms responsible for alteration of transcription [1].

Our purpose was to investigate age-specific RNA production in nerve cells and hepatocytes of F344 and WAG rats differing by narcologic resistance.

MATERIALS AND METHODS

Hepatocytes, superior cervical sympathetic ganglion (SCSG), sensorimotor cortex (SMC), hypothalamic ventromedial nucleus (VMN), and blue spot of 50 F344 and WAG rats aged 1, 6, and 12 months were examined. Surviving slices were incubated routinely [2] with morphine and the protease inhibitor antipaine in the final concentrations in the incubation medium 8 and 0.08 mM, respectively, and ^{3}H-uridine. Control slices were incubated without the agents. The results were expressed as specific radioactivity of slices (cpm/mg wet weight). The method for assessing absolute and relative incorporation of isotope in RNA molecules was described previously [2]. The data were processed using Student's *t* test.

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RESULTS

Our results confirm alteration of transcription activity in the course of individual development [6]. A high level of transcription in comparison with other structures was observed in SCSG of F344 rats aged 1 and 12 months. For WAG rats the same was observed only at the age of 1 month, whereas in 6-month-old animals the highest incorporation of the isotope was noted in SMC neurons (Tables 1 and 2). In control, the values differed in two strains at the age of 1 and 12 months for SCSG and VMN. This confirms genotypic heterogeneity of animals with different sensitivity to narcotics [5,10].

Our findings show that sensitivity of rats to morphine changes with age. In 1-month-old rats of both strains the reactions to morphine were the same in all tests, except SMC; at the age of 6 and 12 months similar effects were observed only in SCSG and

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TABLE 1. Effects of Morphine and Antipaine ^{3}H-Uridine Incorporation in Total RNA of WAG Rat Nerve Cells and Hepatocytes (MTm, % of control)

Age, months	Series	SCSG	SMC	VMN	Blue spot	Hepatocytes
1	Control, CMP/mg	128.76±18.37	68.93±9.21	48.21±0.72	24.67±1.26	48.83±11.48
	Morphine	-50.42*	+143.9*	+10.31	+142.2*	-19.07
	Antipaine	-12.82	+25.95	-8.01	-7.13	-7.66
	Morphine+antipaine	-37.06	+82.52*	-21.66	+60.64	+12.16
6	Control, CMP/mg	42.42±2.98	71.42±16.69	32.37±5.09	44.23±5.24	35.84±5.84
	Morphine	+103.5*	-57.55*	-35.93	+77.44*	-23.24
	Antipaine	-34.82*	-65.04*	+13.81	-43.23*	-25.66
	Morphine+antipaine	-26.87*	-63.99*	-11.96	-33.85	-14.20
12	Control, CMP/mg	28.00±0.40	34.25±3.62	31.67±1.38	15.52±0.15	19.60±4.02
	Morphine	59.90*	-24.67	-22.10*	-4.57	+69.95*
	Antipaine	+36.89*	-59.47*	-37.67*	+50.77	+154.1*
	Morphine+antipaine	+29.82*	-47.91*	+16.99	-19.07	+228.5*

Note. Here and in TABLE 2: Increment (+) and drop (-) in comparison with control; *$p<0.01$ in comparison with control.

TABLE 2. Effects of Morphine and Antipaine ^{3}H-Uridine Incorporation in Total RNA of F344 Rat Nerve Cells and Hepatocytes (MTm, % of control)

Age, months	Series	SCSG	SMC	VMN	Blue spot	Hepatocytes
1	Control, CMP/mg	455.32±58.39	54.80±6.18	24.60±6 53	20.33±4.23	42.77±4.82
	Morphine	-62.71*	+15.89	-12.77	+63.70*	+41.59
	Antipaine	-71.50*	-20.31	+68.37	+102.6*	-32.52
	Morphine+antipaine	-69.59*	-37.19*	+21 42	+21.66	-7.95
6	Control, CMP/mg	48.41±2.62	45.30±7.12	32.30±2 67	30.74±5.55	23.10±3.09
	Morphine	+62.88*	+21.92	+87 40*	-16.14	+43.72*
	Antipaine	-28.26*	+1.24	+24 02	-14.09	+113.3*
	Morphine+antipaine	+23.30	-42.78*	+44 74	-17.08	+168.1*
12	Control, CMP/mg	213.11±48.22	40.69±6.53	13.51±1 42	12.20±3.13	30.79±5.17
	Morphine	-78.51*	-15.56	+0.37	+123.7*	+13.58
	Antipaine	-84.21*	-47.60*	+82.46	+93.39	-20.14
	Morphine+antipaine	-85.15*	-12.98	+8.51	+50.25	+4.61

SMC, respectively. This may be due to quantitative and qualitative changes in transcribed DNA sites during postnatal ontogenesis [6], which is different in these rat strains. Morphine effects on all studied structures were different in different age groups of both strains, except the F344 rat SMC. Antipaine canceled age-dependent changes in SCSG and VMN of F344 rats.

Results of experiments with hepatocytes were of special interest. Reaction of transcription to morphine, antipaine, and combination of both agents was the same in both strains. The drugs potentiated the effects of each other in 12-month-old WAG rats and in 6-month-old F344 rats. It is difficult to draw an unambiguous conclusion from such results.

Data on combined effects of the drugs on the level of transcription indicate a protease mechanism of RNA synthesis regulation during exposure to morphine. Antipaine abolished the morphine effect during exposure of SCSG and VMN neurons of 6-month-old F344 rats to both drugs. Similar results were obtained with SCSG of 1- and 6-month-old WAG rats and with VMN of 12-month-old WAG rats, and with blue spot of 1- and 6-month-old WAG rats and of 1- and 12-month-old F344 rats. In the majority of cases, morphine-induced changes

returned to the control level. It is noteworthy that during combined exposure morphine effect was abolished in the same structures of both strains (SCSG, VMN, and blue spot) but in different age groups. These structures are characterized by a high content of noradrenergic neurons, and VMN contains accumulations of dopaminergic neurons [3]. The morphology and function of opiate system of the brain and noradrenergic and dopaminergic systems are related [4]. Therefore, a protease mechanism can be responsible for changes in transcription in the SCSG, VMN, and blue spot of the studied rat strains during exposure to morphine. However, other mechanisms modifying RNA production are probable, which may change during postnatal ontogenesis.

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