PHYSIOLOGY

Melatonin and Ulceration in Rat Stomach in Acute Emotional Stress

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Formation of peptic ulcers under conditions of acute emotional stress was studied in rats injected with different doses of melatonin (0.5, 1, and 2 mg/kg). The number of total length of peptic ulcers increases under conditions of stress. In unstressed rats melatonin induces ulceration of gastric mucosa. In a dose of 1 mg/kg melatonin exerts protective effect on gastric mucosa. No significant changes in the number and total length of peptic ulcers are noted with 0.5 and 2 mg/kg melatonin.

Key Words: *emotional stress: melatonin: peptic ulcer*

Melatonin (MT) is a component of the stress-protective system of the organism [6]. Synthesis of MT in the pineal gland and in the retina is catalyzed by serotonin- and arylamine-dependent N-acyltransferases [15]. The synthesis and release of MT is rhythmically regulated by suprachiasmatic nuclei of the hypothalamus and corrected by exogenous light-darkness cycle [16].

Biological effects of MT are mediated by pituitary and suprachiasmatic nucleus [9], hypothalamus being a more important trigger structure of autonomic and hormonal regulation. The hypothalamo-reticulo-limbic complex, a potential circuit for long-term circulation of excitation [4], is a morphofunational substrate of so-called sustained excitation responsible for visceral disorders in emotional stress (ES) [1], for instance, ES-induced ulceration in gastric mucosa [8].

The content of MT in the pineal gland and blood serum greatly varies in various types of stress. For instance, γ-irradiation causes a decrease followed by elevation of MT content in the pineal gland [3]. Chronic ES disturbs diurnal rhythm of MT production [12]. Enhanced production of MT has been observed under conditions of rotational stress [11]. Activity of pineal gland, specifically, of β-adrenoreceptors regulating N-acyltransferase activity, decreases after chronic (but not acute) electrical stimulation [7].

Melatonin exhibits antioxidant [14], antiviral [2], and immunomodulating [13] activities. Its immunostimulating effects are observed even under conditions of immunosuppression accompanying ES, drug intoxication, viral infections, and aging [5]. However, the effects of MT on ulceration in the gastric mucosa in ES is little studied.

In the present study we examined the effect of various doses of exogenous MT administered to rats before and after acute ES on stress-induced ulceration of gastric mucosa.

MATERIALS AND METHODS

Experiments were carried out on 120 male Wistar rats weighing 192.2±1.6 g. The animals (4 rats per cage) were maintained at 20-22°C and natural illumination and had free access to food and water.

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The rats were divided into 12 groups, 10 animals per each. They were intraperitoneally injected with physiological saline (PS) or 0.5, 1, and 2 mg/kg MT (freshly dissolved in 1 ml PS) immediately before ES. Control (unstressed) rats received MT or PS 4 h prior to decapitation. In addition, MT in a dose of 1 mg/kg or PS was injected to experimental rats 1 h prior or immediately after ES.

The animals were deprived of food 24 h before experiment and had free access to water. The immersion model was employed to produce ES [10]. The animals were immobilized in plastic boxes (16.5×5.5 cm^2) and immersed into water (23°C) up to the metasternum for 2 h and then returned to their cages for another 2 h. Control rats were left in their cages. Control and experimental animals were decapitated, the stomach was cut along the greater curvature, washed, and the number of ulcers and their total length were evaluated. The data were processed statistically using the Mann-Whitney test and multifactor dispersion analysis (ES/control×MT/PS). The LSD test was used for multiple intergroup comparison.

RESULTS

Control (unstressed) rats injected with PS had no peptic ulcers (Table 1). Intraperitoneal injection of various doses of MT induced ulceration in the gastric mucosa, which was most pronounced with a dose of 1 mg/kg (Table 1). These differences were insignificant.

Acute ES considerably increased the number of peptic ulcers in rats injected with PS 1 h before ES (6-fold, $p<0.03$), immediately before ES (7-fold, $p<0.05$) or immediately after ES (6-fold, $p<0.03$). The total length of peptic ulcers in ES (Table 1) also increased in rats injected with PS ($p<0.016$; $F=6.05$, $d.f.=1$). Thus, the water immersion stress induces ulceration in rat stomach. The intensity of this process (number of ulcers and their total length) does not depend on the time of PS injection.

In animals receiving 0.5 and 2 mg/kg MT, the number of peptic ulcers after ES (Table 1) increased significantly ($p<0.006$, $F=7.98$, $d.f.=1$) in comparison with unstressed rats injected with the same doses of MT (4.3- and 9-fold, respectively, $p<0.05$). The total length of peptic ulcers (Table 1) after ES in rats injected with 0.5 and 2 mg/kg MT was 8.6- and 6.9-fold higher ($p<0.016$, $F=6.05$, $d.f.=1$) than in unstressed rats. The number of peptic ulcers in stressed rats injected with 0.5 and 2 mg/kg MT slightly surpassed that in animals injected with PS, these differences being unsignificant.

In rats exposed to ES, MT in a dose of 1 mg/kg had a protective effect on gastric mucosa. Injection of 1 mg/kg MT 1 h before ES prevented the increase in the number of ulcers in the stomach after ES, while administration of MT immediately and 1 h after ES slightly decreased this parameter in comparison with unstressed animals (1.25-fold, $p<0.006$, $F=7.98$, $d.f.=1$). The number of ulcers after ES in rats injected with 1 mg/kg MT (before, immediately after and 1 was after ES) was lower than in rats injected with PS.

The total ulcerated length (Table 1) in rats injected with 1 mg/kg MT 1 h before and immediately after ES was slightly higher than in unstressed animals (sta-

TABLE 1. Number of Peptic Ulcers and Their Total Length in Rats Exposed to Acute ES after Intraperitoneal Injection of PS or Different Doses of MT (*M±m*)

Injection, dose (mg/kg)	Experimental conditions	Number	Length, mm
PS	Control	0.00±0.00	0 02±0.02
PS	1 h before ES	0.60±0.27*	0.84±0.41
PS	Before ES	0.70±0.37***	1.02±0.67+
PS	After ES	0.60±0.27*	0.49±0 26
MT, 0.5	Control	0.30±0.30	0.31±0.27
MT, 0.5	Before ES	1.30±0.47***	2.66±1.15+
MT, 1	Control	0.50±0.34	0.70±0.49
MT, 1	1 h before ES	0.50±0.22	0.78±0.43
MT, 1	Before ES	0.40±0.22**	0.55±0.30+
MT, 1	After ES	0.40±0.31	0.88±0.79
MT, 2	Control	0.10±0.10	0.08±0.08
MT, 2	Before ES	0.90±0.31***	0.55±0.19**

Note. +$p<0.016$ ($F=6.50$, $d.f.=1$), **$p<0.006$ ($F=7.98$, $d.f.=1$) compared with the control (ANOVA); *$p<0.05$ compared with the control.

tistically insignificant). However, injection immediately before stress reduced 1.27-fold the total length of ulcers in comparison with unstressed animals injected with the same dose of MT ($p<0.016$, $F=6.05$, $d.f.=1$). The total length of peptic ulcers in rats injected with 1 mg/kg MT 1 h or immediately before ES was lower than in stressed animals injected with PS.

Thus, acute ES increased the number and total length of peptic ulcers in rats injected with PS. Ulceration of the gastric mucosa in rats exposed to acute ES is a natural consequence of stress. Intraperitoneal injection of exogenous MT to unstressed animals also induced ulceration of the stomach. Administration of MT to control rats which were not exposed to stress of other adverse factors apparently has a negative effect. Administration of various doses of exogenous MT has unequal effect on ulceration of rat stomach. Administration of 0.5 and 2 mg/kg MT did not protect gastric mucosa against ES-induced ulceration, while in a dose of 1 mg/kg it elicited a pronounced protective effect, which did not depend of the time of injection. On the other hand, this dose maximally induced ulceration in unstressed animals. It can be hypothesized that the dose which produces a protective effect in ES acts as the maximum ulcerogenic dose under normal conditions.

The mechanisms of the effect of MT are a subject of our further experiments.

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