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Effect of Stress on Brain Histamine[1]

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MAZURKIEWICZ-KWILECKI, I. M. AND H. TAUB. *Effect of stress on brain histamine*. PHARMAC. BIOCHEM. BEHAV. 9(4) 465–468, 1978.—Stress of short duration (5 min) resulted in a significant increase in plasma corticosterone level and a significant decrease in the midbrain histamine concentration in rats. Exposure to 15 min stress caused a significant elevation in the hypothalamic histamine level. Stress of longer duration (30 or 60 min) did not affect hypothalamic, cortical or midbrain histamine concentration although plasma corticosterone level remained elevated. Repeated exposures of rats to 15 min stress did not significantly alter histamine concentration of any of the brain regions studied. Plasma corticosterone concentration was only 28% of that observed in animals exposed to single 15 min stress. Present data suggest a role of brain histamine in response to stress.

Histamine Brain Stress Rat Corticosterone

BRAIN biogenic amines were reported to be altered after various types of stress [1, 14, 21, 22]. The possible involvement of the putative central neurotransmitter histamine [5, 15, 16] in some type of stress was investigated with conflicting results reported. A decrease in hypothalamic and cortical histamine concentration and an increased H^3-histamine synthesis following a single ($^1/_2$ hr–2 hr) cold exposure and restraint was found in rats [20]. However, others [11] using the same time of sampling were unable to detect any changes in cerebral histamine concentration in cold exposed or immobilized rats. Moreoever, it was reported [23] that stress induced by restrain led to a decreased turnover of H^3-histamine in the brains of mice. Stress in the form of an electrical shock was shown to increase concentration of histamine in rat hypothalamus and cortex [2]. In contrast, a decrease in hypothalamic and cortical histamine level which was associated with an increase in histidine decarboxylase activity was observed in guinea-pigs subjected to the same type of stress [13].

In view of these conflicting reports, we examined in the present investigation the effects of acute and repeated stress on histamine concentration in several brain regions of rats. Plasma corticosterone was monitored simultaneously as an indication of stressful conditions.

METHOD

Male Sprague-Dawley rats (200–220 g) were housed in metal cages (3 rats per cage) in a temperature controlled room (24°C) with lights on from 7 a.m. to 7 p.m. Stress was induced by a procedure similar to that used in rapid eye movement (R.E.M.) sleep deprivation studies [3]. The rats were placed on a small circular platform (5 cm in diameter and 12 cm in height) centrally located in a tub of water (25°C); the depth of water was 10 cm. The animals were exposed to this procedure for varying periods of time.

In "acute" stress studies, 4 groups of rats were used. Each group was allocated for one time period. Rats were individually placed on the platform for either 5, 15, 30 or 60 min. The animals were sacrificed by decapitation immediately after the stressing procedure. Rats not subjected to stress were used as controls.

In another set of experiments, rats were repeatedly exposed to the same stress for 15 min twice daily for 4 days and sacrificed immediately after the last (eighth) 15 min exposure. It should be noted that all the experiments were so planned that the animals were killed in the afternoon hours (between 1–3 p.m.) when plasma corticosterone was reported to be at its lowest level [19]. Following decapitation blood was collected from the severed neck blood vessels into heparin-containing tubes for corticosterone determination. The brains were rapidly removed, washed with ice-cold saline, blotted and placed on special glass plates kept on ice. Different brain regions were dissected according to a modified method of Glowinski and Iversen [9].

Histamine Determination

The tissues were assayed for their histamine content according to a modification of the double isotope technique of Taylor and Snyder [20]. This procedure depended on the methylation of endogenous histamine in the tissues by added histamine methyltransferase, using S-adenosyl-L-methionine methyl [^{14}C]; (56 mCi/mmole, New England Nuclear) as the methyl donor. A tracer amount of ^{3}H-histamine (5–10 Ci/mmole, New England Nuclear) was added to correct for the varying degree of histamine methylation in different samples. Endogenous S-adenosylmethionine was destroyed by boiling the tissue, a procedure which also served to precipitate protein.

The [^{14}C]-[^{3}H]-methylhistamine and [^{14}C]-methylhistamine were separated from [^{14}C]-S-adenosylmethionine

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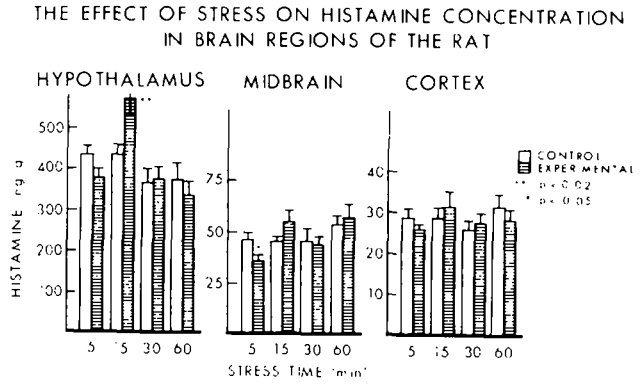

FIG. 1. Time course of stress induced changes in histamine concentration in different brain regions of the rat. The animals were exposed to stress (see methods) for 5, 15, 30 and 60 min and sacrificed immediately after. Nonstressed rats served as controls. The data represent the Mean ± S.E.M. of at least 8 animals in each group. $^{*}p < 0.05$ compared to control values. $^{**}p < 0.02$ compared to control values.

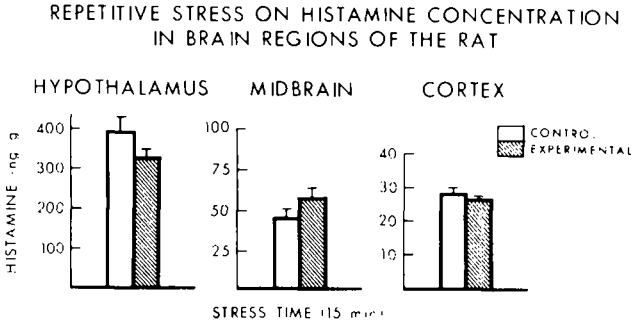

FIG. 3. The effects of repeated stress (15 min twice daily for 4 days) on histamine concentration in brain regions of the rat. The data represent the Mean + S.E.M. of 8 experiments.

and [^{3}H]-histamine by extracting into chloroform from a salt-saturated alkaline solution. The chloroform was evaporated and the residue was taken up into ethanol and scintillation fluid (Econofluor) and counted in a Beckman LS 150 liquid scintillation spectrometer.

Plasma Corticosterone was determined by a slight modification of the method of Givner and Rochefort [8] which is based on the capability of corticosterone to fluoresce in sulfuric acid. The data is reported as μg per 100 ml of plasma ($\mu g\%$).

RESULTS

Histamine concentration in 3 regions of rat brain following single exposure of rats to stress for varying periods of time is demonstrated in Fig. 1. When rats were stressed for 5 min, the histamine concentration was significantly reduced in midbrain (78 + 6% of control). However, 15 min of stress led to a significant increase in hypothalamic histamine concentration (130 ± 9% of control). Longer exposures to stress (30 or 60 min) did not cause significant alterations in any of the brain regions investigated.

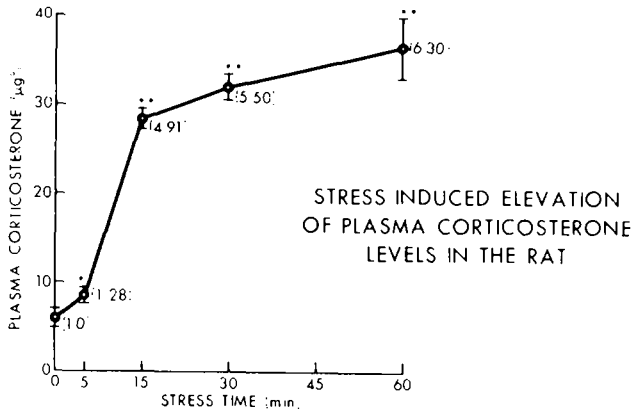

FIG. 2. Time course of stress induced elevation of plasma corticosterone concentration in the rat; $\mu g\%$ refers to μg/100 ml of plasma. Post-stress to pre-stress ratios are indicated in the brackets. The data represent the Mean ± S.E.M. of 8 animals in each group. $^{*}p < 0.05$ compared to control values. $^{**}p < 0.005$ compared to control values.

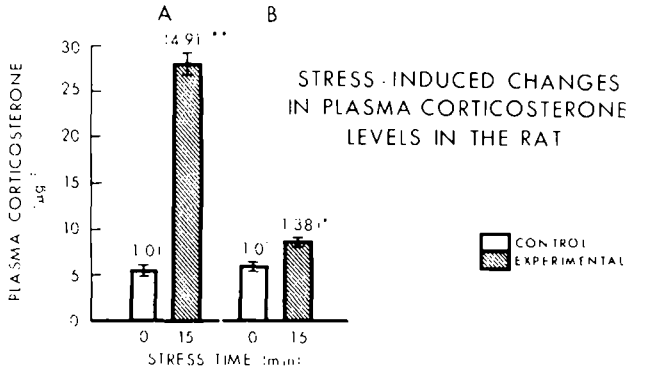

FIG. 4. Plasma corticosterone elevation after single exposure (15 min) to stress (A) and (B) following repeated exposure (15 min twice daily for 4 days); $\mu g\%$ refers to μg/100 ml of plasma. Post-stress to pre-stress ratios are indicated in brackets. The data represents the Mean + S.E.M. of 8 experiments in each case. $^{*}p < 0.05$ compared to control values. $^{**}p < 0.005$ compared to control values.

The time course of stress induced changes in plasma corticosterone levels is indicated in Fig. 2. Significant elevation of plasma corticosterone (128% of control) was noted as early as 5 min after stress; higher levels were reached after 15 min of stress (491% of control) and remained elevated when the stress was maintained for 30 and 60 min (550 and 630% of control respectively).

Repeated exposure of rats to stress (15 min twice daily for 4 days) (Fig. 3) did not significantly alter histamine concentration in any of the brain regions.

Plasma corticosterone levels in rats following a single (A) or repeated 15 min of exposure to stress (B) is demonstrated in Fig. 4. Although the plasma corticosterone level following the multiple schedule was significantly elevated (138% of control) when compared with its respective controls, it was only approximately 1/4 of that observed in rats following a single 15 min of stress.

DISCUSSION

The effectiveness of our procedure as a valid stress producing stimulus was reflected by the rapid elevation in the

levels of plasma corticosterone noted as early as 5 min after the placement of rats on the platform (Fig. 2). Our observations are consistent with the reported significant elevation of plasma corticosterone following brief period of handling or short exposure to a novel environment [18].

In the present studies, stress of short duration (5 min) resulted in a significant decrease in endogenous histamine concentration in the midbrain and a slight non-statistically significant decrease in the hypothalamus and cortex. It is of interest that the existence of a histaminergic pathway emanating from the midbrain or brain stem, ascending through the lateral hypothalamic area and projecting into entire diencephalon has been reported [17]. It was also suggested that the activity of this ascending tract is inhibited during stressful situations [23]. The observed rapidly occuring but short lasting decrease in the midbrain histamine level could have been due to stress induced decrease in histamine synthesis, increased release or increased metabolism. Histamine synthesis could not be investigated since stressful situation associated with intravenous or intraventricular administration of the histamine precursor, histidine, prior to our experimental conditions had to be avoided.

The significant increase in hypothalamic histamine level seen after 15 min of stress is of interest in view of the demonstrated importance of this brain region in response to stress [6]. It is possible that this increase may represent a compensatory change for the slight decrease in this brain region noted after 5 min of stress.

The increase in hypothalamic histamine concentration was associated with approximately a five-fold increase in the plasma corticosterone level when compared to non-stressed rats. Although plasma corticosterone level remained significantly elevated when the rats were subjected to stress of longer duration (30, 45 and 60 min) the histamine concentration was not significantly altered in the hypothalamus nor in any of the other brain regions investigated.

Similar to presently observed changes in brain histamine others found increased histamine level but in cerebral hemispheres and in the brain stem of rats subjected to short lasting electrical shock [2]. The reported decrease in hypothalamic and cerebral histamine level in restrained and cold exposed rats [20] were not confirmed by others [11]. In mice subjected to electrical shock no changes were found in brain histamine concentration [17] although immobilization stress resulted in a decreased histamine turnover [23].

It is possible that the effects of stress on brain histamine concentration depend on the type of stimulus, species used, duration of exposure and the time of sampling. Since a large part of the hypothalamic histamine pool is known to have a very rapid turnover [20], the initial change may not be detectable if the time of sampling is delayed.

In contrast to the effect seen after a first exposure to stressful situations, repeated exposure to the same stress did not significantly change histamine levels in any of the brain regions investigated. Moreover, plasma corticosterone level determined after the last (eighth) exposure to stress although significantly elevated when compared with control rats was only 1/4 of that noted in animals subjected to a single 15 min period of stress. It seems therefore possible that these rats were less stressed because certain adaptation to the initial response may have taken place.

The relationship between corticosteroids and brain histamine is still unknown. Hypophysectomy did not affect hypothalamic histamine levels or the formation of H^3-histamine from intraventricularly administered H^3-histidine in rats [20], however, a decreased synthesis of brain histamine was noted 5 days after adrenalectomy in mice [23]. Stress induced changes in brain histamine turnover in mice were not affected by adrenalectomy [23].

Brain histamine was demonstrated to play a role in a number of physiological events [4, 7, 10, 12]. Our findings suggest possible involvement of brain histamine in the response to stress.

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