Blockade of Corticosterone Synthesis Reduces Serotonin Turnover in the Dorsal Hippocampus of the Rat as Measured by Microdialysis

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Abstract
The influence of plasma corticosterone concentration on serotonin (5-HT) turnover in the dorsal hippocampus was investigated. The experiments were performed in freely moving male Wistar rats in their home cage. Blood samples were taken via a permanent jugular vein catheter to determine plasma corticosterone levels. Extracellular levels of 5-HT and its metabolite 5-hydroxy-indole acetic acid (5-HIAA) were measured using in vivo microdialysis. The rats received an intravenous (i.v.) infusion of the steroid synthesis-inhibitor metyrapone (150 mg/kg/ml) in order to manipulate circulating corticosterone levels. Three hours later, the monoamine oxidase inhibitor pargyline (15 mg/kg/2 ml i.v.) was administered to produce an accumulation of extracellular 5-HT. Pargyline administration led to a four fold increase in 5-HT levels, while reducing 5-HIAA by 45%. Metyrapone pretreatment blocked the pargyline-induced rise in plasma corticosterone to baseline levels and diminished the pargyline-induced increase in 5-HT, without affecting 5-HIAA levels. Thus, the data suggest that a decrease in availability of corticosterone for its receptors by metyrapone diminished the 5-HT synthesis rate. Since plasma corticosterone levels during this blockade are still low, it is assumed that brain glucocorticoid receptor occupation is reduced, while mineralocorticoid receptors are still substantially occupied. Therefore the present results support the hypothesis that corticosterone through glucocorticoid receptor activation enhances 5-HT synthesis rate and release in the dorsal hippocampus.

Mutual interactions between corticosteroid hormones and the serotonergic (5-HT) system in the brain have been documented (1, 2). In the present study we focus on the raphe-dorsal hippocampal 5-HT system (3). Several studies have shown that corticosteroid hormones control the activity of this system. It was found that high amounts of corticosteroid facilitate the stress induced synthesis rate of 5-HT by increasing the catalytic efficiency of tryptophan hydroxylase (4–8). Additionally, 5-HT synthesis rate was reduced after removal of the adrenals (9). Replacement of the adrenalectomized (ADX) rats with corticosterone restored this index for 5-HT turnover, while administration of aldosterone was ineffective (10, 11). These findings suggested that 5-HT biosynthesis is under the stringent control of the naturally occurring glucocorticoid.

The above described effects of corticosteroid hormones were derived from tissue concentrations of 5-HT, in response to a monoamine oxidase (MAO) inhibitor. In the present study, we investigated in intact freely moving animals the dynamic relationship between the level of circulating plasma corticosterone and 5-HT turnover as measured by in vivo microdialysis. Extracellular 5-HT and 5-HIAA levels were measured in the dorsal hippocampus after administration of the MAO inhibitor pargyline (12, 13). In this setup the extracellular 5-HT is a resultant from its synthesis rate and release and can be considered as an index for 5-HT turnover. The 11 β-hydroxylase inhibitor, metyrapone, was used to inhibit corticosterone synthesis and consequently change the availability of circulating corticosterone levels for neural corticosteroid receptors (14). Blood samples were taken for corticosterone measurement via a permanent catheter. The present findings provide additional evidence for the hypothesis that glucocorticoids are important modulators of 5-HT transmission.

Results
The dialysate 5-HT and 5-HIAA values were expressed as the percentage of the baseline prior to pargyline infusion. Baseline concentrations of 5-HT in the dialysate were 21.2 ± 3.4 pg/ml and 35.2 ± 8.1 pg/ml and of 5-HIAA 14.1 ± 1.6 ng/ml and
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Enzyme 11-β-hydroxylase that catalyses the formation of all 11-β-hydroxylated steroids is also necessary for the formation of aldosterone and other 11-β hydroxylated metabolites, the concentration of these substances will also be affected by metyrapone. Metyrapone inhibits the formation of all 11-β hydroxylated steroids from desoxycorticosterone. According to published results) and the glucocorticoid receptor antagonist, RU38486, reduce fear-enhanced anxiety behavior in the elevated-plus-maze (42). These anxiolytic actions may also be due to a reduction of 5-HT neurotransmission. It is hypothesized that metyrapone, GR antagonists and 5-HT1A receptor agonists exert their anxiolytic action via a common pathway, i.e., inhibition of tryptophan hydroxylase activity and 5-HT synthesis in the dorsal raphe nucleus, resulting in diminished extracellular 5-HT levels in limbic forebrain areas, e.g., dorsal hippocampus.

In conclusion, the present findings support the hypothesis that high circulating corticosteroid levels stimulate 5-HT turnover. 5-HT is then available in increased quantities to supply an agonist, administered into the dorsal raphe nucleus, diminished anxiolytic action via a common pathway, i.e., inhibition of tryptophan hydroxylase activity and 5-HT synthesis in the dorsal raphe nucleus, resulting in diminished extracellular 5-HT levels in limbic forebrain areas, e.g., dorsal hippocampus.

Materials and methods

Animals
Fifteen male Wistar rats, weighing between 400–550 g were used. They were individually housed in clear plexiglas cages (25 × 25 × 30 cm) on a 12-h light-dark regimen (lights on between 08.00 h—20.00 h) at a room temperature of 21 ± 2 °C. All animals had free access to standard food (Hope Farms rat chow) and water.

Surgery
Surgery was performed under halothane anaesthesia. A silicon catheter (0.95 mm o.d., 0.50 mm i.d.) was inserted into the right jugular vein for drug infusion and blood sampling (47). The microdialysis guide was stereotaxically implanted just above the dorsal hippocampus (guide tip at AP −3.6, L+1.4, V−2.0; ref. points bregma and top of the dura, according to Paxinos & Watson (48)). The microdialysis guide and the


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