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Activation of 5-HT_2 receptors induces glycogenolysis in the rat brain

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Abstract

The effect of 5-HT_2 receptor activation on brain glycogen and the extracellular concentration of glucose was investigated in the present study. An injection of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) (2 mg/kg, i.p.) or mescaline (10 mg/kg, i.p.) at an ambient temperature of 29 °C produced a 35–45% decrease in brain glycogen that persisted for at least 2 h. DOI also increased the extracellular concentration of glucose in the striatum by 60%. Maintenance of rats at 22 °C significantly attenuated DOI-induced glycogenolysis, as well as DOI-induced hyperthermia, and the increase in the extracellular concentration of glucose in the striatum. DOI-induced hyperthermia, glycogenolysis and increase in the extracellular concentration of glucose also were attenuated in rats treated with the 5-HT_2 receptor antagonist, 6-methyl-1-(methylethyl)-ergoline-8β-carboxylic acid 2-hydroxy-1-methylpropyl ester maleate (LY-53,857) (3 mg/kg, ip). These results support the conclusion that 5-HT_2 receptor activation promotes glycogenolysis and that hyperthermia exerts a prominent role in this process.

Keywords: 5-HT_2 receptor; DOI; Glycogenolysis; Hyperthermia

1. Introduction

Glycogen is the single largest energy reserve in the brain and is localized mainly in astrocytes (Lajtha et al., 1981). Glycogen concentrations in the brain are highly coupled with neuronal activity (Magistretti et al., 1993). The glycogen content of the brain has been shown to be affected by pharmacological, as well as physiological, manipulations. A breakdown in brain glycogen has been demonstrated by administration of amphetamines, as well as by subjecting rats to high (32 °C) or low (10 °C) environmental temperatures (Hutchins and Rogers, 1970).

Several studies in recent years have demonstrated that the glycogen content in the brain is regulated by several neurotransmitters, neuropeptides and ions. Potassium ions have been shown to induce glycogenolysis in astroglial enriched cell cultures of rat cerebral cortex (Cambray-Deakin et al., 1988) and in mouse cerebral cortical slices (Hof et al., 1988). Sorg and Magistretti (1991) have demonstrated glycogenolysis induced by norepinephrine, adenosine and vasoactive intestinal peptide in primary cultures of mouse cerebral cortical astrocytes. Adenosine and vasoactive intestinal peptide also have been shown to induce glycogenolysis in mouse cerebral cortical slices (Magistretti et al., 1981, 1986).

In addition, Quach et al. (1982) reported that 5-HT stimulates glycogenolysis in slices of cerebral cortex and that the effect of 5-HT was attenuated by desipramine and iprindole. Among the pharmacological properties of iprindole and desipramine is a modest affinity for the 5-HT_2 receptors (Palvimaki et al., 1996). Furthermore, Poblete and Azmitia (1995) have reported that 1-(2,5-dimethoxy-4-bromophenyl)-2-aminopropane (DOB), a 5-HT_2 receptor agonist, activates glycogen phosphorylase in vitro.

The purpose of the present study was to examine the effect of 5-HT_2 receptor agonists on glycogenolysis in vivo and to assess the potential role of hyperthermia in this response. Extracellular concentrations of glucose in the brain also were assessed by in vivo microdialysis.

2. Materials and methods

2.1. Animal procedures

Adult male rats (200–275 g) of the Sprague–Dawley strain (Charles River, Portage, MI) were used in the studies.

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The animals were housed three per cage in a temperature (22–24 °C) and humidity controlled room with a 12/12-h light/dark cycle and allowed food and water ad libitum. Animals undergoing surgery were housed one per cage, post operatively. On the day of the experiment, rats were placed in an environment maintained at 28–29 °C for 2 h prior to the administration of DOI, with the exception of one experiment in which rats were maintained at a normal ambient temperature of 22–24 °C. A temperature of 28–29 °C was maintained with the use of heaters in the experimental room (8×10 ft^2). All procedures were in strict adherence to the National Institutes of Health guidelines and approved by the institutional animal care committee.

2.2. Chemicals, drugs and drug treatment

(±)-1-(2,5-Dimethoxy-4-iodophenyl)-aminopropane hydrochloride (DOI), mescaline hydrochloride and 6-methyl-1-(methylethyl)-ergoline-8β-carboxylic acid 2-hydroxy-1-methylpropyl ester maleate (LY-53,857) were obtained from Sigma (St. Louis, MO). All the drugs were dissolved in 0.15 M NaCl. NADP disodium salt, hexokinase, glucose-6-phosphate dehydrogenase and amyloglycosidase were purchased from Roche Diagnostics (Chicago, IL). All reagents used in the assay were prepared as described by Nahorski and Rogers (1972).

2.3. Biochemical measurements

2.3.1. Glycogenolysis

Rats were killed by decapitation and the brains were rapidly removed from the skull and immersed in liquid nitrogen within 12–15 s. The cerebellum was separated from the rest of the brain, and the tissue was stored at −80 °C until analysis. Procedures for the analysis of glycogen were similar to those described by Nahorski and Rogers (1972). Brain tissue (approximately 250 mg) consisting of the caudal quarter of the left cerebral hemisphere (including the hypothalamus, thalamus, and temporal cortex and midbrain) was weighed and homogenized in 3 ml of 0.03 N HCl at 0 °C. The homogenate was placed in boiling water for 5 min. Assay tubes contained 300 μl of acetate buffer (pH = 4.6), 100 μl of the homogenate or glycogen standard and 10 μl of amyloglycosidase or water. The tubes were vortexed and incubated at room temperature for 30 min. After incubation, 1.33 ml Tris buffer (pH = 7.8), 0.66 ml $MgCl_2 \cdot 6H_2O$ (2 mg/ml), 100 μl ATP (2 mg/ml) and 10 μl NADP (10 mg/ml) were added to each tube. The tubes were vortexed and subjected to centrifugation at $10{,}000 \times g$ for 5 min. The supernatants were transferred to other tubes, and the fluorescence (excitation 350 nm/emission 460 nm) was measured in a fluorescence spectrophotometer (Model: F-2000, Hitachi Instruments, Naperville, IL). Hexokinase (10 μg/10 μl) and glucose-6-phosphate dehydrogenase (2 μg/10 μl) were then added, and the tubes were vortexed and incubated at room temperature for 30 min. The fluorescence was again measured. The difference in the fluorescence values was corrected for sample, reagent and enzyme blank. Glycogen values are reported as glucose equivalents (μmol/g tissue). The glycogen values reported in the present study, albeit within the range of literature values, may underestimate actual glycogen concentrations due to the use of rapidly dissected tissue from decapitated rats. Concentrations of glycogen from microwave fixed rats recently have been reported to exceed those reported here (Kong et al., 2002).

2.3.2. Glucose analysis

Glucose in the dialysis samples was assayed using a modified method of the glycogen assay (Nahorski and Rogers, 1972). Assay tubes contained 1.33 ml Tris buffer (pH = 7.8), 0.66 ml $MgCl_2 \cdot 6H_2O$ (2 mg/ml), 100 μl ATP (2 mg/ml), 10 μl NADP (10 mg/ml) and 20 μl of dialysate sample or glucose standard. The tubes were vortexed and fluorescence of the sample was measured as described above. Hexokinase (10 μg/10 μl) and glucose-6-phosphate dehydrogenase (2 μg/10 μl) were added, and the tubes were vortexed and incubated at room temperature for 30 min prior to fluorescence determination. Glucose values were calculated as mM and expressed as percent of the baseline values. Glucose in plasma was determined by the glucose oxidase–peroxidase method using a commercially available product.

2.4. In vivo microdialysis procedures

Rats were implanted with a stainless steel guide cannula under ketamine/xylazine (70/6 mg/kg, i.m.) induced anesthesia 48–72 h prior to the insertion of the dialysis probe. On the day of the experiment, a concentric style dialysis probe was inserted through the guide cannula into the striatum. The coordinates for the tip of the probe were A, 1.2 mm; L, 3.1 mm; V, −7.0 mm from bregma, according to the stereotaxic atlas of Paxinos and Watson (1986). The microdialysis probes were constructed as described previously (Yamamoto and Pehek, 1990). The dialysis surface of the membrane (Spectra Por, 6000 molecular weight cut-off, 210 μm outside diameter) was 4.5 mm in length to allow for analysis of the entire dorso ventral striatum. The probe was connected to an infusion pump set to deliver glucose free Dulbecco's phosphate buffered saline containing 1.2 mM $CaCl_2$ at a rate of 1.8 μl/min. After a 2-h equilibration period, dialysis samples were collected every 30 min. At least three baseline samples were obtained prior to drug treatment.

2.5. Body temperature measurements

Separate groups of rats were used for the determination of drug effects on body temperature. On the day of the experiment, the rats were allowed to acclimate in their cages at 28–29 or 22–24 °C for 2 h before body temperatures

were measured. Measurements of rectal temperature were made using a telethermometer and a thermister probe. The probe was lubricated with a small amount of petroleum jelly and inserted 5 cm into the rectum of each rat where it remained for at least 30 s, until a stable temperature was obtained. LY-53,857 (3 mg/kg, i.p.) was administered 30 min prior to administration of DOI (2 mg/kg, i.p.). Measurements were taken every 30 min for a 1-h period prior to administration of DOI and for a 1.5-h period following the injection of the drug. The change in body temperature was determined by subtracting the body temperature at time 0 from the maximal body temperature recorded after DOI administration.

2.6. Statistical analysis

The effects of DOI and mescaline on brain glycogen were analyzed with a one way analysis of variance (ANOVA). The effects of ambient temperature and the 5-HT_2 receptor antagonist LY-53,857 on DOI-induced glycogenolysis were analyzed with a two way ANOVA. Glucose data from dialysis experiments were analyzed with a two way repeated measures ANOVA. Multiple pairwise comparisons were performed using the Student–Newman–Keuls test. Treatment differences for all the data were considered statistically significant at $P<0.05$.

3. Results

Significant reductions in brain glycogen concentrations were evident following the systemic administration of the 5-HT_2 receptor agonist DOI (2 mg/kg, i.p.) to rats maintained at 29 °C (Fig. 1). Brain glycogen concentrations were reduced by 42% ($P<0.05$) 1 h following the administration of DOI. Significant ($P<0.05$) reductions in the brain concentration of glycogen were evident within 30 min of DOI administration and persisted for at least 2 h. Mescaline (10 mg/kg, i.p.), another 5-HT_2 receptor agonist, also produced a reduction of 35% in the brain concentration of glycogen (vehicle, 2.64 ± 0.11 vs. mescaline, 1.72 ± 0.08 μmol of glucose eq./g tissue; $P<0.05$).

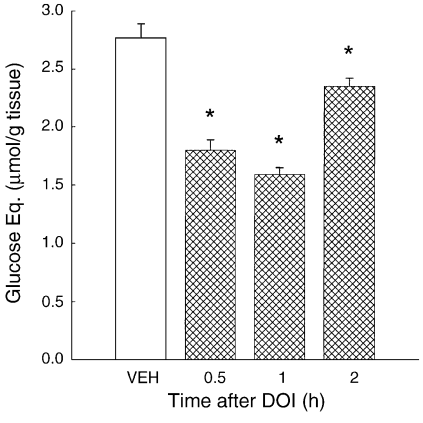

Fig. 1. Effect of DOI on glycogen content in brain. Rats were injected with DOI (2 mg/kg, i.p.) or vehicle and killed at the indicated times following drug treatment. The values represent the mean ± S.E. of 5–6 rats and are expressed in terms of μmol glucose liberated from glycogen per gram of tissue. *$P<0.05$ compared with vehicle (VEH)-treated rats.

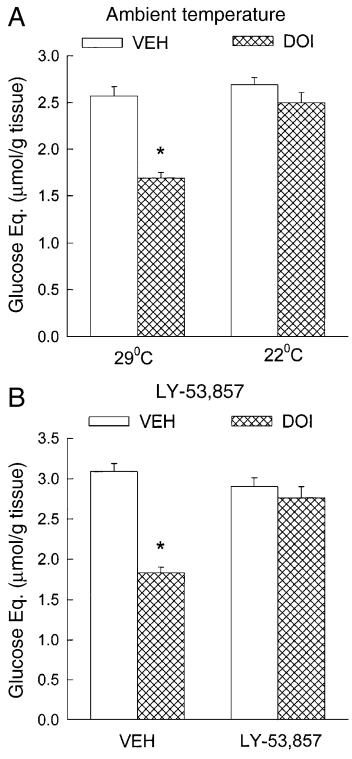

Fig. 2. Effect of ambient temperature or LY-53,857 on the DOI-induced glycogen depletion. (A) Rats were maintained at an ambient temperature of 29 or 22 °C for 2 h prior to administration of DOI (2 mg/kg, i.p.), or vehicle (VEH) and the animals were killed 30 min after drug treatment. (B) LY-53,857 (3 mg/kg, i.p.) was injected 30 min prior to administration of DOI (2 mg/kg, i.p.). The values represent the mean ± S.E. of 5–6 rats. *$P<0.05$ compared with VEH-treated rats.

The extent to which DOI produced glycogenolysis was dependent upon the ambient temperature at which the drug was administered. Maintenance of rats at 22 °C for 2 h prior to the administration of DOI markedly attenuated DOI-induced glycogenolysis when compared to the response of rats maintained at 29 °C. Whereas the administration of DOI (2 mg/kg, i.p.) resulted in a 35% reduction ($P<0.05$) in the brain concentration of glycogen in rats maintained at 29 °C, DOI had no significant effect on brain glycogen in rats maintained at 22 °C (Fig. 2A). The alteration of ambient temperature alone did not significantly affect brain glycogen content.

The effect of the 5-HT_2 antagonist LY-53,857 on the DOI-induced depletion of brain glycogen in rats maintained at 29 °C is shown in Fig. 2B. DOI-induced glycogenolysis was completely abolished ($P<0.05$) in LY-53,857-treated rats. Treatment with LY-53,857 alone did not significantly alter brain glycogen content.

Attenuation of DOI-induced glycogenolysis by maintenance of rats at 22 °C or by the administration of the 5-HT_2 receptor antagonist LY-53,857 was associated with a suppression of DOI-induced hyperthermia. At a warm ambient temperature of 29 °C, the administration of DOI (2 mg/kg, i.p.) increased the body temperature of rats by 1.6 ± 0.2 °C (N = 12). In rats maintained at an ambient temperature of 22–24 °C, DOI failed to significantly alter body temperature (0.0 ± 0.1 °C, N = 6). Moreover, the hyperthermic response to DOI in rats pretreated with LY-53,857 (3 mg/kg, i.p.) was only 0.2 ± 0.1 °C, which was significantly less (P < 0.05) than the response of 1.5 ± 0.17 °C for rats treated only with DOI (N = 6).

In addition to the evaluation of the effects of DOI on the brain concentration of glycogen, the effect of DOI on the extracellular concentration of glucose in the striatum was investigated using in vivo microdialysis. The systemic administration of DOI (2 mg/kg, i.p.) to rats at 29 °C resulted in an immediate and sustained increase (P < 0.05) of 50–65% in the concentration of glucose in dialysis samples from the striatum (Fig. 3A). The concentration of glucose in the dialysis samples remained elevated for at least 3 h following the administration of DOI. However, maintenance of rats at 22 °C for 2 h prior to the administration of DOI and throughout the dialysis period prevented the DOI-induced increase in glucose concentration in the striatum (Fig. 3A). There was no significant difference in the extracellular concentration of glucose in the striatum of rats simply maintained at 22 or 29 °C. In separate groups of rats, it was determined that DOI treatment did not modify the concentration of glucose in plasma from peripheral blood (vehicle, 97 ± 7 mg/dl vs. DOI, 105 ± 6 mg/dl).

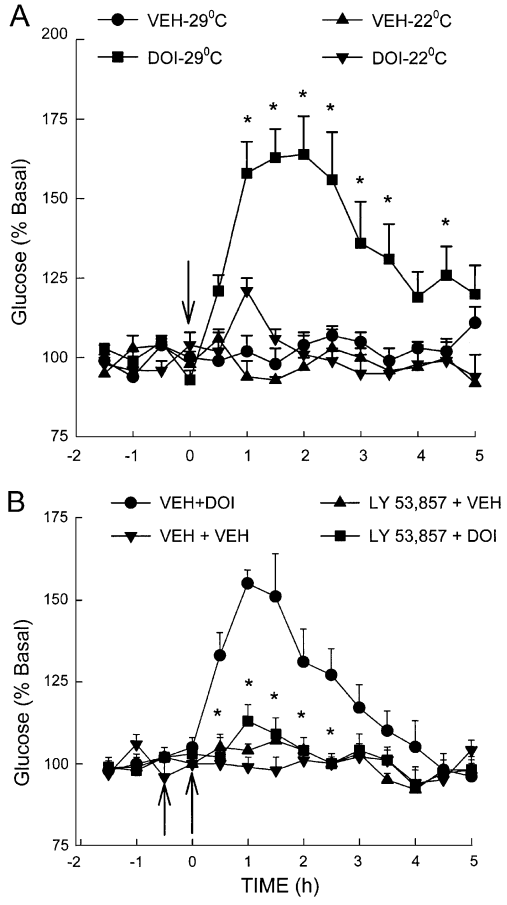

Fig. 3. Effect of ambient temperature or LY-53,857 on the DOI-induced increase in the concentration of glucose in dialysis sample of the striatum. (A) A single injection of DOI (2 mg/kg, i.p.) or vehicle (VEH) was administered at time 0 as marked by the arrow at 29 or 22 °C. The values represent the mean ± S.E. of 5–6 rats. *P < 0.05 compared with VEH-treated rats. There were no significant differences in the values for vehicle- and DOI-treated rats kept at 22 °C. The basal concentrations for extracellular glucose at time 0 for rats maintained at 22 and 29 °C were 0.3 ± 0.03 and 0.28 ± 0.02 mM respectively. (B) DOI (2 mg/kg, i.p.) or vehicle was administered at time 0 (as marked by the arrow) to rats that had been injected with LY-53,857 (3 mg/kg, i.p.) or vehicle 30 min earlier at −0.5 h. The values represent the mean ± S.E. of 5–6 rats. *P < 0.05 compared to values for rats treated with vehicle (VEH) + DOI.

Administration of the 5-HT_2 receptor antagonist LY-53,857 (3 mg/kg, i.p.) also markedly attenuated (P < 0.05) the DOI-induced increase in the glucose concentration in dialysis samples of the striatum (Fig. 3B). Glucose concentrations in samples from rats treated with LY-53,857 and DOI did not differ from those in rats treated with LY-53,857 and vehicle. Administration of LY-53,857 alone did not significantly alter the glucose concentration in the dialysis samples.

4. Discussion

In a previous study, MDMA (3,4-methylenedioxymethamphetamine), a 5-HT releasing agent (Nash and Gudelsky, 1996), was shown to induce glycogenolysis (Darvesh et al., 2002). The additional finding of Darvesh and co-workers that the 5-HT_2 antagonist LY-53,857 prevented MDMA-induced glycogenolysis was supportive of the view that 5-HT_2 receptor activation promotes glycogenolysis. In the present study, the administration of DOI, a 5-HT_2 receptor agonist (Marek and Aghajanian, 1996), resulted in a rapid decrease in brain glycogen that persisted for at least 2 h. In addition, mescaline, a structurally dissimilar hallucinogen and 5-HT_2 receptor agonist (Newton et al., 1996), also promoted glycogenolysis in the rat brain. These data are consistent with the hypothesis that activation of 5-HT_2 receptors induces glycogenolysis in the rat brain. In further support of this conclusion is the finding that the administration of LY-53,857 attenuated DOI-induced glycogenolysis in rat brain.

Data from in vitro studies also are supportive of a role of 5-HT_2 receptors in promoting glycogenolysis. Quach et al. (1982) demonstrated that 5-HT enhances glycogen breakdown in slices of mouse cerebral cortex, and that iprindole and desipramine, which show affinity for the 5-HT_2 receptor in the 100–200 nM range (Palvimaki et al., 1996), attenuate 5-HT-induced glycogenolysis in cortical slices in vitro. Poblete and Azmitia (1995) have shown that 5-HT and

MDMA, as well as DOB, a selective 5-HT_2 receptor agonist, increase the activity of glycogen phosphorylase, which is the rate limiting enzyme in glycogenolysis, in astroglia rich primary culture. In addition, the 5-HT_2 antagonist mianserin was shown to attenuate the 5-HT- and MDMA-induced increases in the activity of glycogen phosphorylase (Poblete and Azmitia, 1995).

Hutchins and Rogers (1970) have reported that maintenance of rats at 32 °C, which presumably results in an elevated body temperature, results in a breakdown of brain glycogen. In the present study, DOI-induced glycogenolysis was accompanied by an increase in body temperature of approximately 1.6 °C. This is in accord with previous documentation of 5-HT_2 receptor-mediated hyperthermia (Gudelsky et al., 1986). Administration of the 5-HT_2 antagonist LY-53,857 not only attenuated the DOI-induced hyperthermia, but also attenuated DOI-induced glycogenolysis. An environmental manipulation (e.g., maintenance of rats at 22 °C) also prevented DOI-induced hyperthermia, as well as DOI-induced glycogenolysis. Thus, pharmacological or physiological antagonism of DOI-induced hyperthermia was accompanied by attenuation of the glycogen response to DOI. These findings support the conclusion that hyperthermia plays a major role in the 5-HT_2 receptor mediated breakdown of glycogen. The possibility that 5-HT_2 receptors may not directly regulate glycogen formation/breakdown but rather modulate energy regulation through alterations in body temperature contrasts with an apparent direct action of 5-HT and 5-HT_2 agonists to induce glycogenolysis in vitro (Quach et al., 1982), perhaps through activation of glycogen phosphorylase (Poblete and Azmitia, 1995).

Concentrations of brain glycogen have been reported to be reduced following exposure of rats to either warm or cold environmental temperatures (Hutchins and Rogers, 1970). Thus, glycogen content may not be reflective of brain metabolic activity, since cerebral glucose utilization has been shown to be increased and decreased by hyperthermia and hypothermia, respectively (McCulloch et al., 1982). Hutchins and Rogers (1970) have suggested that the reduction in brain glycogen due to changes in body temperature may be part of a stress response.

The administration of DOI also resulted in an increase in the extracellular concentration of glucose in the striatum, as judged from glucose concentrations in dialysis samples. Pharmacological (e.g., LY-53,857) or environmental (e.g., 22 °C) manipulations that attenuated the DOI-induced decrease in brain glycogen also attenuated the DOI-induced increase in the extracellular concentration of glucose in the striatum. Although these findings are correlational in nature, they are suggestive of the possibility that the DOI-induced increase in the extracellular concentration of glucose is the result of glycogenolysis. However, the activity of glucose-6-phosphatase, the enzyme involved in the formation of glucose from glycogen, is extremely low in the brain. Thus, it may be unlikely that sufficient glucose is formed in the process of glycogenolysis to account for the increase in extracellular glucose.

Brain glucose is heavily dependent on glucose supplied through the blood (Lund-Anderson, 1979). However, it is unlikely that the increase in extracellular glucose in brain is due to increased peripheral glucose, since glucose in peripheral plasma was unaltered by DOI treatment.

An alternative mechanism underlying the DOI-induced increase in extracellular glucose in brain may be related to glucose transport. Hyperthermia has been reported to increase the tissue/blood glucose concentration ratio (Carlson et al., 1976). Thus, DOI-induced hyperthermia may accelerate glucose transport into brain. Glucose transport would have to be increased to a considerable extent inasmuch as glucose utilization in the striatum has been reported to be increased in response to hyperthermia (McCulloch et al., 1982).

The results of the present study are supportive of the view that 5-HT_2 receptor activation promotes glycogenolysis in vivo. Moreover, hyperthermia, through an unidentified mechanism, appears to play a critical role in mediating the 5-HT_2 receptor regulation of cellular energetics.

Acknowledgements

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