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Gamma-Hydroxybutyrate and Cocaine Administration Increases mRNA Expression of Dopamine D_1 and D_2 Receptors in Rat Brain

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The effects of acute and repeated gamma-hydroxybutyrate (GHB) and cocaine administration on D_1 and D_2 dopamine receptor mRNA expression were examined using in situ hybridization histochemistry in different rat brain structures rich in GHB receptors. Six hours after a single GHB administration (500 mg/kg IP), an increase in D_1 and D_2 mRNA expression was observed in almost all regions examined; whereas, acute cocaine injection (20 mg/kg IP) had no effect. Repeated exposure to GHB (500 mg/kg IP twice daily) for 10 days, followed by a 14-h withdrawal period, induced increasing effects on D_1 and D_2 dopamine receptor mRNA expression, similar to those caused by chronic treatment with cocaine (20 mg/kg IP once a day). These effects of GHB and cocaine on dopamine receptor mRNA expression could be a consequence, for both compounds, of the modulation of dopaminergic activity; thus, supporting the benefit of GHB in cocaine substitution therapy. ***[Neuropsychopharmacology 21: 662–669, 1999]*** *© 1999 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.*

KEY WORDS: *GHB (γ-hydroxybutyrate); Cocaine; D_1 and D_2 dopamine receptors mRNA; In situ hybridization; Rat brain*

Gamma-hydroxybutyrate (GHB) is a brain metabolite of GABA, which has been postulated to play a role as a neuromodulator (Vayer et al. 1987). GHB possesses high-affinity receptors that are present only in neurons with a restricted specific distribution in the hippocampus, cortex, and dopaminergic structures of the rat brain (Hechler et al. 1992). Its interaction with such neurotransmitter systems as GABA, serotonin, opiates, and dopamine has been reported (Roth et al. 1980, for review see Maitre 1997). The GHBergic system controls the dopaminergic activity mainly by reducing impulse flow in nigrostriatal and mesocorticolimbic pathways, thereby regulating firing and dopamine release (Roth et al. 1973). Following an initial attenuation of extracellular dopamine levels, GHB induces a stimulation of tyrosine hydroxylase activity and an increase in dopamine release in the striatum and dopaminergic corticolimbic structures (Maitre 1997).

GHB was originally described as a general anesthetic and hypnotic agent (Laborit 1964) and has been used clinically in the treatment of narcolepsy (Mamelak et al. 1986). More recently, GHB was shown to alleviate both ethanol and opiate withdrawal syndromes in humans successfully (Gallimberti et al. 1992, 1993) and to decrease self-administration of cocaine in the rat (Martellotta et al. 1998). Recent observations in humans also suggest a possible abuse liability of GHB (Chin et al. 1992; Galloway et al. 1997), although the development of tolerance to, or dependence on, massive and chronic doses of GHB was not reported during narcolepsy

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treatment (Mamelak et al. 1986). In the rat, GHB is not self-administered and cannot serve as a positive reinforcer in phencyclidine self-administration (Beardsley et al. 1996), but GHB displays potential rewarding properties (Martellotta et al. 1997).

Much of the behavioral and reinforcing potential of psychostimulant drugs is related to alterations in dopaminergic transmission in striatal and mesocorticolimbic structures (Koob 1992). Cocaine potentiates dopamine neurotransmission by blocking dopamine reuptake. Repeated cocaine administration produces a subsensitivity of dopamine autoreceptors, an adaptative mechanism that contributes to increasing dopamine neuron activity in the ventral mesencephalon and to enhancing dopamine release in striatal areas (Ackerman and White 1990; Kuhar et al. 1991).

Because GHB and cocaine share the ability to stimulate dopaminergic transmission by enhancing striatal extracellular dopamine concentration, and because both compounds may be abused in humans, the present study was intended to examine whether their repeated administration produces common changes in dopamine D_1 and D_2 receptor mRNA expression.

MATERIAL AND METHODS

Male Wistar rats (Janvier, France) weighing 250 to 300 g were housed two per cage on a 12/12 h light/dark cycle (light on at 7:00 h), with free access to food and water. Gamma-hydroxybutyrate, sodium salt (Sigma, St. Louis, MO) and cocaine hydrochloride (Sigma) were dissolved in sodium chloride 0.9% and injected intraperitoneally (IP, 2 ml/kg). Control animals were injected with NaCl 0.9%. For acute treatment, GHB (500 mg/kg) and cocaine (20 mg/kg) were administered 6 h before sacrifice of the animal. In the case of chronic treatment, GHB (500 mg/kg) was injected twice per day (9:00 h, 19:00 h) and cocaine (20 mg/kg) was injected daily (19:00 h) for 10 days. Sacrifice and brain extraction were carried out 14 h after the last injection.

Probes were synthetic single-strand oligo-deoxynucleotides (IGBMC, Strasbourg, France). D_1R: 45 mers: 5′-dGGT GGT CTG GCA ATT CTT GGC GTG GAC TGC TGC CCT CTC CAA GGC-3′ (Zhou et al. 1990); the D_2 receptor probe was a mixture of two 45-base synthetic oligo-deoxynucleotides (Bunzow et al. 1988; Le Moine et al. 1990): D_2R_1: 45 mers: 5′-dCCC ATT GAA GGG CCG GCT CCA GTT CTG CCT CTC CAG ATC GTC ATC-3′ and D_2R_2: 45 mers, 5′-dGGC AAT CAT GAC AGT AAC TCG GCG CTT GGA GCT GTA GCG TGT GTT-3′. The probes (2 pmol D_1R, D_2R_1, D_2R_2) were labeled with 50 μCi [α-^{35}S]deoxy-adenosine-triphosphate (1,300 Ci/mmol, NEN, France) and terminal-deoxynucleotidyl transferase (50–100 U, Boehringer Mannheim France, S.A.) in a 100 mM potassium cacodylate buffer, pH 7.2, containing 2 mM $CoCl_2$ and 0.2 mM dithiothreitol. The labeled probes were separated from free nucleotides by chromatography on Sephadex G25 microcolumns (STE SELECT™-D, TEBU France). The specific activities averaged 5 to 20 Ci/mmol. Specificities of the probes were tested with a 100-fold excess of unlabeled probes in the hybridization medium.

Brain extractions were carried out between 9:00 and 11:00 A.M.. Rats were anesthetized with ketamine (Imalgene®, Rhône Mérieux France, 100 mg/kg IP) and perfused through the heart with 1% paraformaldehyde. The brains were excised, immersed for 1 h in the same fixative at 4°C and then in phosphate buffer 0.2 M containing 15% sucrose for 20 h, frozen in liquid isopentane (−40°C) and stored at −80°C until used. Frozen brains were sectioned (12 μm) on a cryostat (Reichert-Jung), and thaw-mounted on gelatin-coated slides. Sections were subsequently stored at −80°C until hybridization. Adjacent sections were used for D_1R and D_2R probe hybridization. Before hybridization, the sections were warmed to room temperature for 10 min, then placed in 0.25% acetic anhydride in 0.1 M triethanolamine/0.9% NaCl, pH 8 for 10 min. After three rinses in 2 × SSC (20 × SSC = 3 M NaCl, 300 mM sodium citrate, pH 7.2), the slides were dehydrated through graded ethanol baths (50, 70, 90, and 100%) before being air dried.

Labeled probes were added to the hybridization medium containing 50% formamide, 0.6 M NaCl, 10 mM Tris pH 7.5, 1 mM EDTA, 1 × Denhardt's solution (0.02% ficoll, 0.02% polyvinylpyrrolidone, 0.02% bovine serum albumin), 500 μg/ml yeast t-RNA, 250 μg/ml denatured herring sperm DNA, 1 mM dithiothreitol, and 10% dextran sulfate. A volume of 35 μl of the probe was added to each slide, and the sections were hybridized under siliconed cover-slips sealed with Gluk rubber for 16 h at 35°C in a humid environment. Following hybridization, the cover-slips were removed, and the sections were washed in two 10-min rinses of 4 × SSC, followed by a 15-min rinse in 1 × SSC at room temperature and two 15-min rinses in 0.5 × SSC at 45°C. The sections were subsequently rinsed with 2 × SSC, dehydrated in graded ethanol and air dried, before being applied to a β-max hyperfilm (Amersham, France) for 3 to 7 days at room temperature. A standard curve was generated for all experiments by quantification of [^{14}C] autoradiographic standards (Amersham, France) laid on each film.

Film images were digitized using a laser scanning densitometer (BIORAD, GS700; 900 dpi). Optical densities (OD) of the different regions were measured, and the background signal from the film was subtracted for each measurement. A total of three to six sections were quantified per circumscribed region (the whole dorsal striatum from AP = 1.7 to AP = −0.8 relative to the bregma, frontal cortex from AP = 2.7 to AP = 1.2, olfactory tubercles from AP = 2.2 to AP = 1.2, and hippoc-

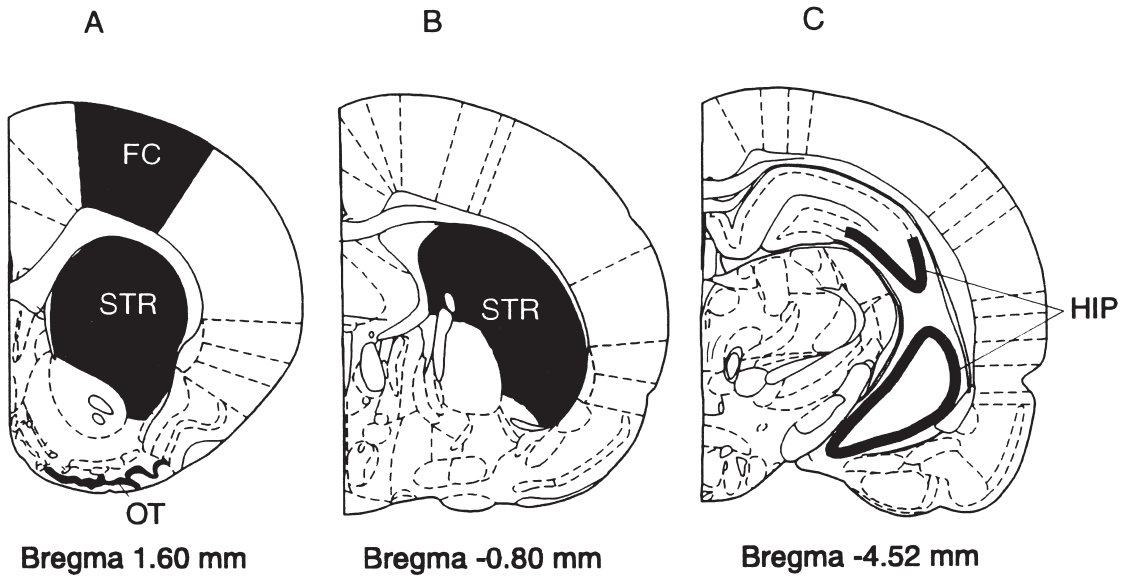

Figure 1. Coronal sections **A**, **B**, and **C** represent the areas of dorsal striatum (STR), frontal cortex (FC), olfactory tubercles (OT), and hippocampus (HIP) that were separately quantitated using computer-assisted image analysis for the D_1 and D_2 dopamine receptor mRNAs (modified from Paxinos and Watson 1986).

ampus from AP = −4.16 to AP = −4.7 in coronal sections, Figure 1). A mean OD was calculated per animal. The values obtained were then converted to μCi/mg wet weight of tissue using the standard curve generated by co-exposed [^{14}C]standards, averaged, and analyzed by the nonparametric Kruskal–Wallis test followed by Dunn's test for multiple comparisons (InStat II, GraphPad Software Inc. 1993).

RESULTS

Six hours after a single cocaine administration (20 mg/kg IP), no significant change in the D_1 or D_2 dopamine receptor mRNA expression was found in any structure examined (Figures 2A, 3A, 4). Conversely, acute GHB administration (500 mg/kg IP) induced increases in D_1 dopamine receptor mRNA levels that were greater in the dorsal striatum (+60%, $p < .01$) and frontal cortex (+60%, $p < .01$) when compared to the olfactory tubercles (+40%, ns) or hippocampus (+40%, ns) (Figure 2A). On the other hand, increases in D_2 dopamine receptor mRNA levels were lower in the striatum (+30%, $p < .05$) and frontal cortex (+35%, $p < .05$) than in the olfactory tubercles (+55%, $p < .01$) and hippocampus (+45%, $p < .05$) (Figure 3A).

Fourteen hours after the last injection of a 10-day chronic cocaine treatment, an increase in D_1 and D_2 dopamine receptor mRNA expression was observed in the different regions (Figures 2B, 3B, 5). D_1 dopamine receptor mRNA induction was higher in the whole dorsal striatum (+75%, $p < .001$) and frontal cortex (+60%, $p < .001$) than in the olfactory tubercles (+35%, ns) or hippocampus (+20%, ns); whereas, D_2 dopamine receptor mRNA expression in response to cocaine was greater in the hippocampus (+95%, $p < .01$) and cortex (+70%, $p < .01$) than in the striatum (+40%, $p < .01$) and olfactory tubercles (+45%, $p < .05$). Chronic GHB administration for 10 days also led to increases in D_1 and D_2 dopamine receptor mRNA levels that were comparable to those observed after repeated cocaine administration (Figures 2B, 3B, 5) in the dorsal striatum (+40%, $p < .05$ for D_1 and +20%, $p < .05$ for D_2), frontal cortex (+60%, $p < .01$ for D_1 and +30%, $p < .05$ for D_2) and olfactory tubercles (+40%, ns for D_1 and +40%, $p < .05$ for D_2). There was no significant increase in dopamine receptor transcripts in the hippocampus after chronic GHB treatment. No significant differences were found between GHB- and cocaine-treated groups in any structure examined.

DISCUSSION

The present study examined the effects of acute and repeated administration of GHB on D_1 and D_2 dopamine receptor mRNA expression in rat brain structures known to express high densities of GHB receptors; that is, dorsal striatum, frontal cortex, olfactory tubercles, and hippocampus (Hechler et al. 1992). The effects of GHB on dopamine receptor mRNA levels were analyzed, taking the effects of the indirect dopamine agonist cocaine as a reference, because both compounds are known to potentiate dopaminergic transmission, at

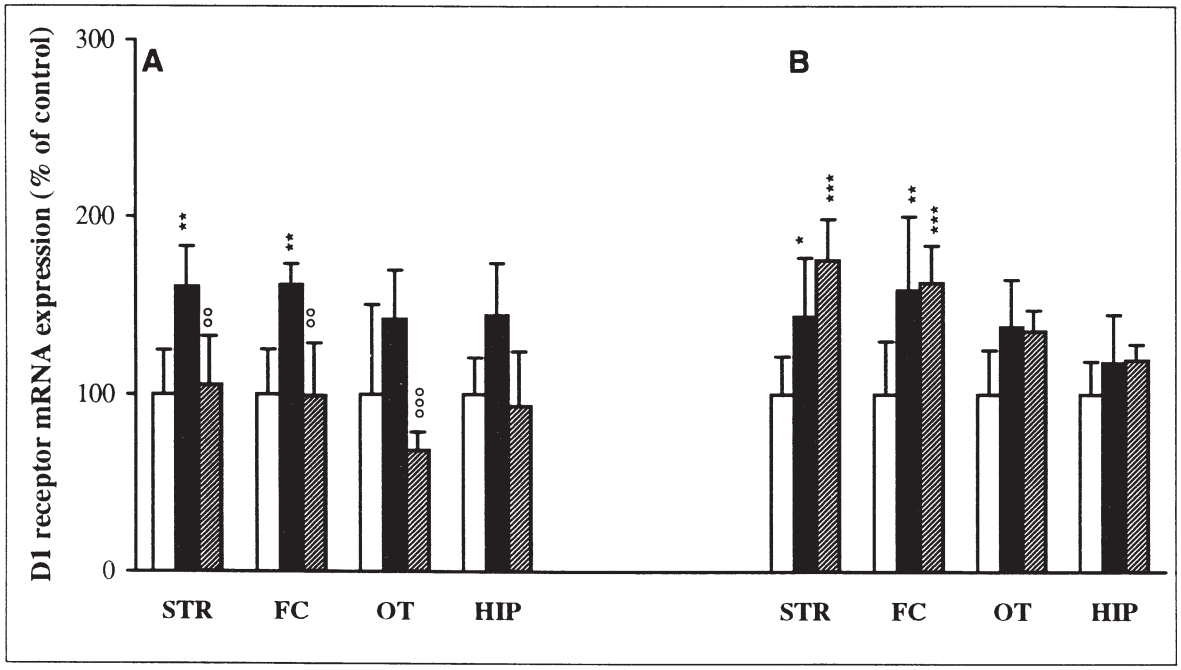

Figure 2. Effects of acute **(A)** and repeated **(B)** administration of either GHB (solid bars) or cocaine (hatched bars) on D_1 dopamine receptor mRNA levels in the striatum (STR), the frontal cortex (FC), the olfactory tubercles (OT), and the hippocampus (HIP). The mRNA levels are expressed as percentage changes relative to levels in saline-injected controls (open bars). The absolute values for controls, expressed in μCi/mg wet weight of tissue, are respectively: 110.2 ± 27.5 (STR), 128.8 ± 32.6 (FC), 256.8 ± 130.2 (OT), 272.4 ± 56.5 (HIP) after acute experiment (A) and: 204.9 ± 43.7 (STR), 268.7 ± 80.3 (FC), 367.6 ± 91.2 (OT), 400.9 ± 73.8 (HIP) after chronic treatment (B). Data are the means ± SEM derived from three rats per treatment group. (*$p < .05$, **$p < .01$, ***$p < .001$ vs. control; °°$p < .01$, °°°$p < .001$ vs. GHB.)

least in the striatum. Moreover, a recent report argues for a role of GHB in decreasing cocaine self-administration in the rat (Martellotta et al. 1998), thus some possible common mechanisms could be involved in a prolonged use of both compounds.

Acute GHB administration induced a significant increase in D_1 and D_2 dopamine receptor mRNAs; whereas, no modification of these messengers was found 6 h after acute injection of cocaine. As regards the acute effect of cocaine, these results are in agreement with previously reported data on D_2 dopamine receptor expression that did not show any variation of D_2 mRNA in the striatum, nucleus accumbens, or prefrontal cortex (Sorg et al. 1995; Spyraki and Sealfon 1993). Regarding D_1 dopamine receptor mRNA expression, this is the first study reporting the effect of acute administration of cocaine. The discrepancies between cocaine- and GHB-induced effects on D_1 and D_2 dopamine receptor mRNA expression may result from a different time course or dose effect exhibited by the two compounds. The GHB-induced dopaminergic stimulation may be delayed or prolonged, as compared to the cocaine-induced dopaminergic stimulation. The difference may also stem from the fact that cocaine is a dopamine reuptake blocker, and GHB is a dopamine releaser; therefore, triggering different extracellular dopamine kinetics. As demonstrated by microdialysis studies, the increased striatal dopamine release has been shown to last longer after GHB administration (Hechler et al. 1991) than after cocaine injection (Hurd and Ungerstedt 1989), although the administration route was different, and the rats were freely moving in the first study and halothane-anesthetized in the latter. A short-term dopamine receptor agonist stimulation may induce receptor desensitization with a reversible loss of ligand binding activity (Kleven et al. 1990; Henry and White 1991; Laurier et al. 1994; Qin et al. 1994). An increase in receptor mRNA secondary to an enhanced transcription of the receptor gene, rather than an alteration of mRNA turnover, was described in the early phase of agonist-induced desensitization (Laurier et al. 1994). Consistent with the lack of changes in D_1 and D_2 mRNA levels that we observed after acute cocaine administration, previous reports did not show any variation of D_1 or D_2 dopamine receptor binding activity (Tsukada et al. 1996; Jung and Bennett 1996). Although no data are available concerning the dopamine receptor binding activity following acute GHB administration, such positive feedback between the receptor and the expression of its gene may be a means of compensating for a decrease in the availability of membrane receptors induced by agonist stimulation. At the dose used in our

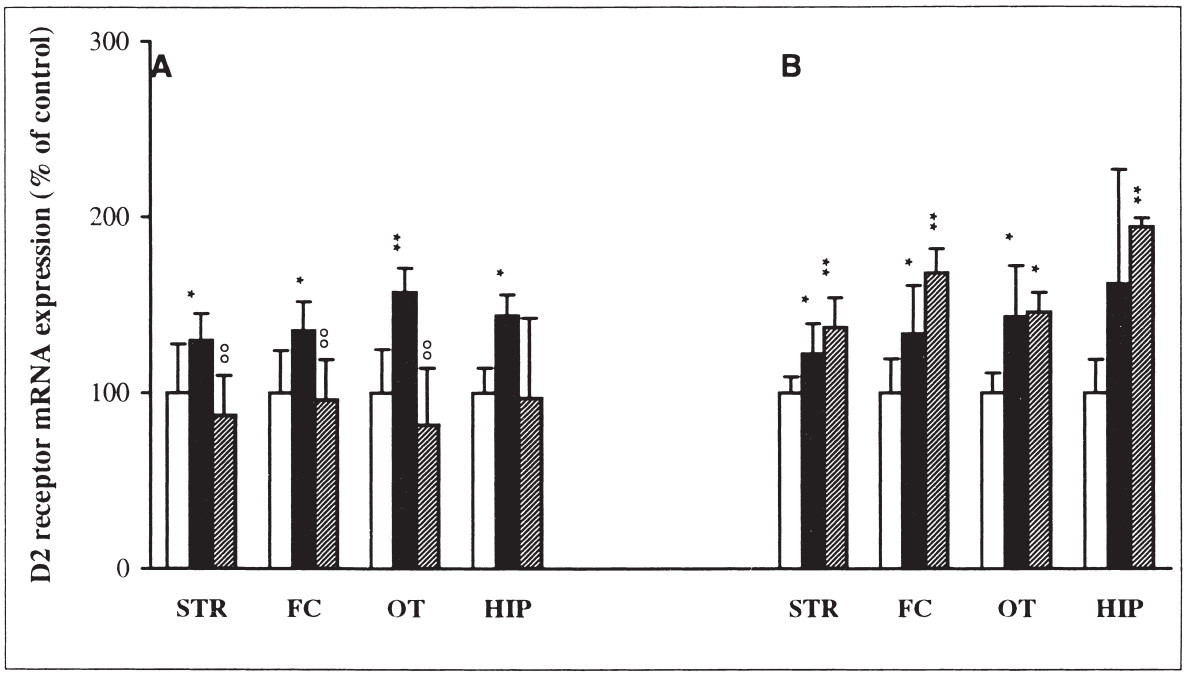

Figure 3. Effects of acute **(A)** and repeated **(B)** administration of either GHB (solid bars) or cocaine (hatched bars) on D_2 dopamine receptor mRNA levels in the striatum (STR), the frontal cortex (FC), the olfactory tubercles (OT), and the hippocampus (HIP). The mRNA levels are expressed as percentage changes relative to levels in saline-injected controls (open bars). The absolute values for controls, expressed in μCi/mg wet weight of tissue, are respectively: 209.9 ± 57.9 (STR), 204.5 ± 48.9 (FC), 224.7 ± 54.8 (OT), 285.6 ± 54.8 (HIP) after acute experiment (A) and: 403.1 ± 35.9 (STR), 373.6 ± 71.4 (FC), 539.2 ± 60.9 (OT), 483.8 ± 91 (HIP) after chronic treatment (B). Data are the means ± SEM derived from three rats per treatment group. ($^*p < .05$, $^{**}p < .01$ vs. control; $^{\circ\circ}p < .01$ vs. GHB.)

experiment (500 mg/kg IP), GHB was, indeed, shown to induce a strong increase in striatal dopamine release, reaching six times the basal value and lasting about 4 hours after injection (Hechler et al. 1991). Thus, 6 h after acute administration of GHB, the extracellular dopamine has been back to the baseline level for 2 h. During this period, a relative hypostimulation of the dopamine receptors may induce a compensatory increase of mRNA expression for these receptors.

Repeated exposure to either GHB or cocaine induced a similar increase in D_1 and D_2 dopamine receptor mRNA expression in different brain structures. The results concerning the cocaine effects are consistent with those of Laurier et al. (1994), who reported an increased synthesis of both dopamine receptor mRNAs in the forebrain and limbic regions. In addition, D_2 dopamine receptor mRNA expression was shown to be increased in the olfactory tubercles after chronic cocaine treatment (Spyraki and Sealfon 1993). This rise in dopamine receptor mRNAs was installed within 24 h after the last injection of cocaine but was normalized 1 week after the termination of drug exposure (Laurier et al. 1994, Spyraki and Sealfon 1993). Increased dopamine efflux has been demonstrated for several days following repeated exposure to cocaine (Kuhar and Pilotte 1996; Peris et al. 1990). Thus, the dopamine receptors are subjected to repeated variations in extracellular dopamine concentrations, possibly leading to modifications of receptor affinity and sensitivity, and of receptor mRNA expression. However, because the present study only analyzes the levels of dopamine receptor mRNA, it should be interpreted with caution in terms of receptor activity. Whereas a short-term dopamine receptor agonist stimulation may induce receptor desensitization, upon longer agonist exposure, proteolytic degradation of receptors occurs, leading to down-regulation. Recovery from agonist-induced receptor down-regulation is slow and seems to require de novo protein synthesis (Buckland et al. 1992; Qin et al. 1994). Previous evidence of alterations in dopamine receptor binding sites following repeated exposure to cocaine has been equivocal. In general, however, no change or a transient reduction in D_2 dopamine binding sites and no change or a delayed decrease in D_1 binding sites have been reported after chronic cocaine treatment (Peris et al. 1990; Kleven et al. 1990; Laurier et al. 1994; Tsukada et al. 1996; Kunko et al. 1998). The profound changes in receptor stimulation resulting from repeated excess of dopamine efflux may be expected to have significant effects, not only on receptor binding sites, but also on receptor

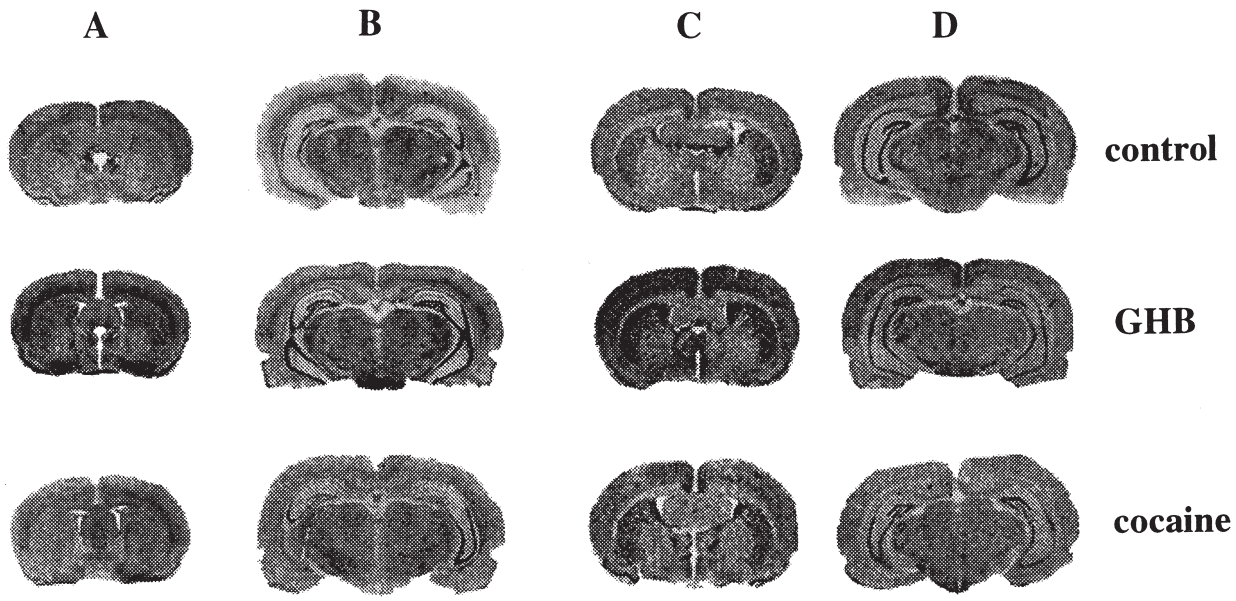

Figure 4. Autoradiograms from coronal rat brain sections processed for in situ hybridization with [^{35}S]-labeled probes selective for D_1 **(A, B)** or D_2 **(C, D)** dopamine receptor mRNAs. Labeling is shown after acute treatment with saline (control), GHB (500 mg/kg IP) or cocaine (20 mg/kg IP).

mRNA expression and on protein turnover. The increase in D_1 and D_2 dopamine receptor mRNA levels that we observed 14 h after the last injection of cocaine or GHB may precede the receptor protein synthesis required for the recovery from down-regulation, because the rate of synthesis of a specific protein is directly related to the level of its corresponding mRNA present in a cell. The rate of synthesis of a receptor may be a more important factor when studying the effects of a drug at a molecular level than the number of receptors available for ligand binding when there is a high level of receptor turnover attributable to high levels of ligands. Therefore, we only examined specific mRNA level coding for the dopamine D_1 and D_2 receptors following

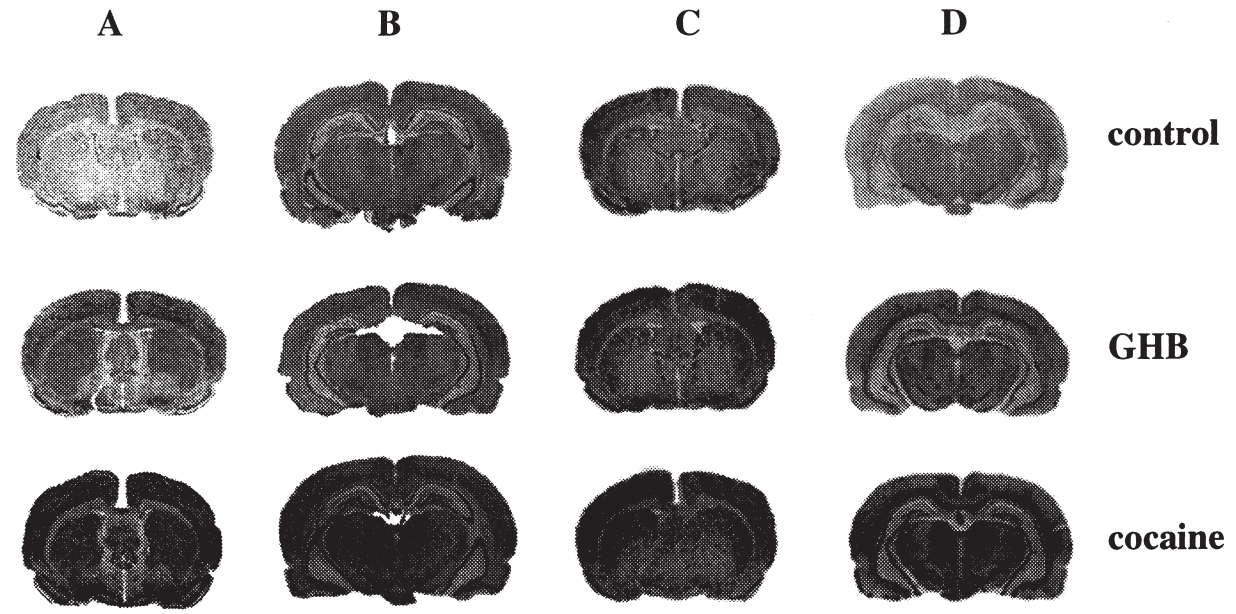

Figure 5. Autoradiograms from coronal rat brain sections processed for in situ hybridization with [^{35}S]-labeled probes selective for D_1 **(A, B)** or D_2 **(C, D)** dopamine receptor mRNAs. Labeling is shown 14 h after the last injection of a chronic exposure to saline (control), GHB (500 mg/kg IP twice a day for 10 days) or cocaine (20 mg/kg IP daily for 10 days).

GHB and cocaine treatment, and the present study did not explore the regulation of dopamine binding sites after these treatments. Evidently, the changes in dopamine receptor mRNAs might matter, even if actual receptor numbers are not altered. The rise in mRNA levels may allow for more rapid turnover of receptor protein, although steady-state receptor numbers do not change. Alternatively, a decrease in extracellular dopamine upon GHB withdrawal cannot be ruled out, although, as has been described after ethanol withdrawal (Diana et al. 1993). In that case, the enhancement of dopamine receptor mRNA synthesis may be an adaptative compensatory mechanism consecutive to hypostimulation of these receptors. In conclusion, repeated exposure to GHB or cocaine resulted in similar rises in dopamine receptor mRNA synthesis. At this state of the study, it is difficult to ascertain whether a common mechanism does occur in the prolonged used of GHB and cocaine. However, this common effect of both compounds on D_1 and D_2 receptor transcripts could, in part, contribute to explaining why GHB may behave as a maintenance medication in cocaine addiction.

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