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European Journal of Pharmacology 306 (1996) 257–264

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Dopamine receptor gene expression in hippocampus is differentially regulated by the NMDA receptor antagonist MK-801

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Received 7 December 1995; revised 15 February 1996; accepted 5 March 1996

Abstract

Glutamate agonists have been shown to stimulate the release of dopamine in the striatum, while the NMDA receptor antagonist MK-801 has been shown to cause an increase in extracellular dopamine in the hippocampus. The effects of MK-801 treatment on dopamine receptor gene expression in the hippocampus are largely unknown. To begin to address this question, we treated rats with 0.3, 1.0, and 3.0 mg/kg of MK-801 daily for 1 week, and measured the mRNAs encoding all five of the dopamine receptors in the hippocampus. MK-801 caused changes in dopamine D_1, D_2, D_3, and D_4 receptor gene expression in a complex manner that suggests that dopamine receptor gene expression in the hippocampus may be differentially regulated by glutamate, via the NMDA receptor. These findings may have implications both for understanding the pathophysiology and modifying treatment of schizophrenia.

Keywords: Glutamate; Dentate gyrus; Dizocilpine; In situ hybridization; Schizophrenia

1. Introduction

Dopamine is the neurotransmitter most often implicated in the pathogenesis of schizophrenia (Snyder, 1976; Seeman et al., 1976). Amphetamine can cause psychotic symptoms, such as delusions and hallucinations, in normal adults, and antipsychotic medications are dopamine receptors antagonists, leading some to theorize that excessive dopaminergic tone contributes to the symptoms of schizophrenia. Unfortunately, the dopamine hypothesis of schizophrenia is inadequate, as complete dopaminergic blockade is only partially antipsychotic, provides limited therapeutic benefits, and does not explain the negative (deficit) symptoms of schizophrenia. Because of these limitations in explaining symptom production and treatment in schizophrenia, other candidate neurotransmitters have been proposed, including glutamate.

Glutamate receptors have been considered as possible substrates of psychotic symptom production and/or modulation in schizophrenia. There are four families of glutamate receptors, including the three ionotropic receptor families: α-amino-3-methylisoxazole-4-propionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) (Hollmann and Heinemann, 1994). Manipulation of the NMDA receptors, in particular, can result in psychotic symptoms. Specifically, the dissociative anaesthetics, which are NMDA receptor antagonists, can produce a syndrome in otherwise normal humans that resembles both the positive and negative symptoms of schizophrenia (Domino and Luby, 1973; Javitt and Zukin, 1991; Krystal et al., 1994). Dissociative anaesthetics also can exacerbate psychotic symptoms in schizophrenics (Luby et al., 1962; Itil et al., 1967). On the other hand, facilitation of glutamate function may have therapeutic benefits. Glycine and D-cycloserine, both agonists for the strychnine-insensitive glycine binding site on the NMDA receptor, have been reported to improve the negative symptoms of schizophrenia (Javitt et al., 1994; Goff et al., 1995).

Postmortem studies have also examined possible glutamate receptor involvement in schizophrenia. NMDA and kainate binding sites are increased in the frontal and temporal cortices of schizophrenics (Nishikawa et al., 1983; Deakin et al., 1989; Ishimaru et al., 1994), and stimulated glutamate release from synaptosomes from the brains of schizophrenics is decreased in the presence of NMDA or kainate (Sherman et al., 1991). These data have been interpreted to suggest that schizophrenia may be associated with decreased glutamatergic activity, mediated by NMDA

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PII S0014-2999(96)00204-X

or kainate receptors. Given that the manipulation of both dopaminergic and glutamatergic systems in the brain can produce psychotic symptoms, the potential interaction of these two systems might represent an important mediator of the symptoms of schizophrenia.

Theories have been generated that implicate both glutamate and dopamine in the pathogenesis of schizophrenia (Carlsson and Carlsson, 1990; Grace, 1993). Modifications of the dopamine hypothesis of schizophrenia have been advanced that propose differential expression of dopaminergic tone within discrete circuits; specifically, an increase in striatal tone and a decrease in frontal cortical tone have been suggested (Davis et al., 1991). This differential dopaminergic tone has been theorized to be linked by glutamatergic projections from the prefrontal cortex to the striatum (Carlsson and Carlsson, 1990; Grace, 1993).

Manipulation of glutamate systems has been shown to modulate dopamine in specific regions of the brain. Glutamate receptor agonists, including *N*-methyl-D-aspartate (NMDA), have been shown to stimulate striatal dopamine release (e.g. Giorguieff et al., 1977; Roberts and Sharif, 1978), which can be attenuated by competitive antagonists (e.g. Araneda and Bustos, 1989; Clow and Jhamandas, 1989). These data suggest that glutamatergic corticostriatal terminals synapse on the midbrain dopaminergic fibers projecting to the striatum, facilitating dopamine release via stimulation of NMDA receptors. This results in a circuit with outflow to the thalamus via the globus pallidus, or what has been proposed as the cortico-striato-pallido-thalamic circuit (Carlsson and Carlsson, 1990).

Much effort has focused on the cortico-striato-pallido-thalamic circuit, but positron emission tomography studies examining striatal function in schizophrenia have not confirmed that alterations of metabolic activity in the striatum are involved in symptom production (Tamminga et al., 1992; Wolkin et al., 1994). Though Wolkin et al. (1994) did not compare the hippocampi of schizophrenics and normal controls, Tamminga et al. (1992) did find hippocampal hypometabolism in schizophrenics, suggesting that the hippocampus may be involved in the production of schizophrenic symptomatology.

Data from other studies have also implicated the hippocampus in the pathogenesis of schizophrenia. Schizophrenics tend to display impairment in hippocampal functions like memory (Kolb and Whishaw, 1983; Gruzelier et al., 1988) and have significant neuroanatomical changes in the hippocampus (e.g. Kovelman and Scheibel, 1984; Bogerts et al., 1985; Altschuler et al., 1990; Benes et al., 1991; Akbarian et al., 1993; Squires et al., 1993). Several studies have demonstrated significant changes in the glutamatergic system in the hippocampi of schizophrenics (Kerwin et al., 1988, 1990; Deakin et al., 1989; Harrison et al., 1991; Eastwood et al., 1995). The hippocampus may be a reasonable region in which to examine the interaction of glutamate and dopamine, particularly given that converging lines of evidence implicate this neuroanatomical region and these neurotransmitters in schizophrenia.

There are several studies that support the possible interaction of dopamine and glutamate in the hippocampus. The hippocampus has a rich dopaminergic innervation (Scatton et al., 1980; Ferraro et al., 1991; Gasbarri et al., 1994; Goldsmith and Joyce, 1994), and utilizes glutamate as its primary intrinsic neurotransmitter. NMDA decreases dopamine release in the hippocampus (Whitton et al., 1994), while the noncompetitive NMDA receptor antagonist MK-801 causes an increase in extracellular dopamine, and the dopamine metabolite HVA, in hippocampus (Whitton et al., 1992). Little is known about dopamine-glutamate interactions at the receptor level in the hippocampus. Given that the relationship of these two neurotransmitters within the hippocampus may be of considerable significance, we have begun to address the interaction of dopamine and glutamate in the hippocampal formation, by investigating the effects of MK-801 on dopamine receptor gene expression.

2. Materials and methods

Adult, male Sprague-Dawley rats (250 g) were housed three to five to a cage, with food and water ad libitum. Animals were injected subcutaneously with either 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg of MK-801, or sterile H_2O vehicle for 7 days ($n = 7–10$ animals per dose). 24 h after the last injection, the animals were killed, and their brains were immediately removed, and frozen in isopentane. The brains were stored at −80°C until sectioned.

Each brain was thawed for 30 min to a temperature of −15°C, and mounted for cryostat sectioning. Using a defined atlas (Paxinos and Watson, 1982) 15 mm sections were obtained throughout each brain, and thaw-mounted on polylysine-subbed microscope slides. The slides were desiccated and stored at −80°C until used for in situ hybridization.

Riboprobes were synthesized from linearized plasmid DNA, as has been previously described (Meador-Woodruff et al., 1991, 1992, 1994). The D_1 insert is 530 base pairs, while the D_2 insert is 495 base pairs (Meador-Woodruff et al., 1991). The D_3 and D_4 riboprobe are synthesized from 326 bp and 447 bp inserts, respectively (Meador-Woodruff et al., 1992), and the D_5 insert is 650 bp (Meador-Woodruff et al., 1994).

7.5 μl of [^{35}S]UTP was added to 5.0 μl 5 × transcription buffer, 2.0 μl 0.1 M dithiothreitol (DTT), 1.0 μl each of 10 mM ATP, CTP, and GTP, 4.5 μl H_2O, 1.0 μl linearized plasmid DNA, 1.0 μl RNase inhibitor, and 1.0 μl RNA polymerase enzyme and incubated for 1.5–2 h at 37°C. 1.0 μl DNase (RNase free) (1 mg/ml) was then added, and the mixture was incubated for 15 min at room temperature. The reaction mixture was sieved through a 1 ml syringe containing G-50 Sephadex equilibrated in Tris

buffer (100 mM Tris-HCl, 12.5 mM EDTA, 150 mM NaCl, and 0.2% SDS, pH 8.0), and 100 μl fractions were eluted.

Four slides per animals were removed from −80°C storage and placed in 4% (w/v) formaldehyde at room temperature for 1 h. The slides were then washed in 2 × SSC (300 mM NaCl/30 mM sodium citrate, pH 7.2) three times and placed in proteinase K (1 μg /ml in 50 mM EDTA/100 mM Tris-HCl, pH 8.0) for 30 min at 37°C. The slides were then washed in double distilled (dd) H_2O for 1 min before being placed in 0.1 M triethanolamine, pH 8.0/acetic anhydride, 400 : 1 (v/v), on a stir plate, for 10 min. The final wash was in 2 × SSC buffer for 5 min, followed by dehydration through graded alcohols and air drying. A cover slip with 30 μl of radiolabelled probe (10^6 dpm)/75% formamide buffer/0.01 M dithiothreitol was placed on each slide. Slides were placed in a covered tray with filter paper saturated with 75% formamide, and incubated at 55°C overnight.

The next day the cover slips were removed and the slides were placed in 2 × SSC for 5 min, followed by RNase (200 μg/ml in 10 mM Tris-HCl, pH 8.0/0.5 M NaCl) at 37°C for 30 min. The slides then underwent the following washes: 2 × SSC at room temperature for 10

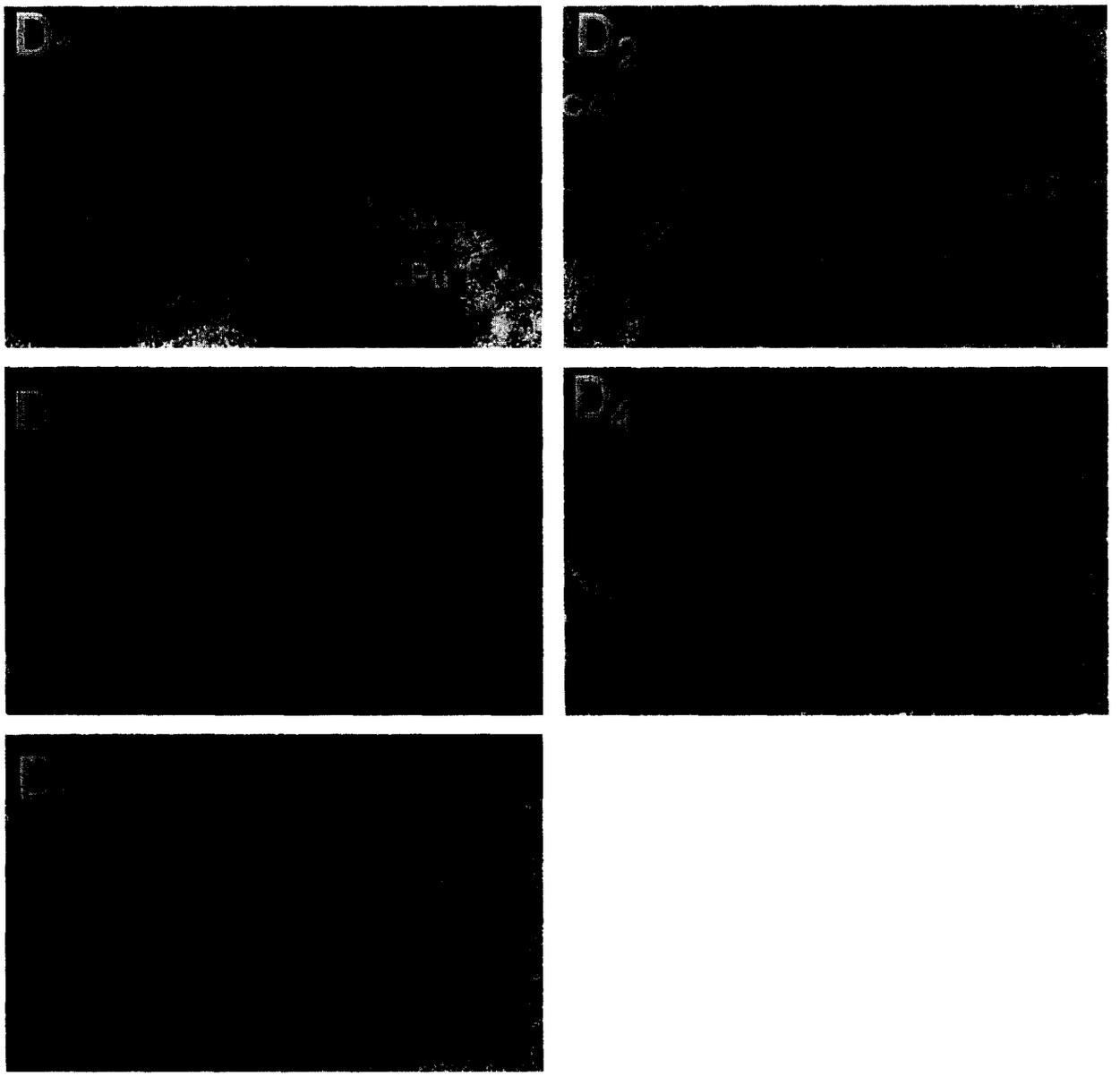

Fig. 1. Distribution of the five dopamine D_{1-5} receptors visualized in the hippocampal formation. The ventral aspect of the granule cell layer of the dentate gyrus (DG) was the only structure labelled by the D_1 probe, while the other four dopamine receptor subtypes were visualized in the entire extent of the granule cell layer of the dentate gyrus, as well as in the pyramidal cell layer of all the subfields of the hippocampus. The thalamus (Th) and the caudate-putamen (CPu) are also labelled by the D_1 probe.

min; 1 × SSC for 10 min at room temperature; 0.5 × SSC at 55°C for 60 min; and 0.5 × SSC for 10 min at room temperature. The slides were dehydrated in graded ethanol solutions and air dried. They were placed in X ray cassettes and apposed to Kodak XAR-5 film for 2–4 weeks. The film was developed and used for quantitative, Macintosh-based computer image analysis (with NIH Image 1.56), as previously described (Meador-Woodruff et al., 1991). Tissue background was subtracted from total gray scale values of labelling in the hippocampal formation, which included the granule cell layer of the dentate gyrus and the pyramidal cell layer of the four subfield (CA1–4) of the hippocampus. The gray scale values were converted into optical density. The average optical density values for each region of each animal was generated from eight measures (left and right sides) of the four slides selected per animal. Comparisons of the average optical densities of the hippocampal structures were examined using one way (D_1) and two way (D_2–D_5) analysis of variance, and post-hoc analyses were made using a Bonferroni/Dunn correction.

3. Results

The distribution of dopamine receptor mRNAs in the hippocampal formation (Fig. 1) was similar to that reported in previous studies (Meador-Woodruff et al., 1991, 1992). Labelling for dopamine D_1 receptors was observed in the ventral aspect in the granule cell layer of the dentate gyrus. The other four mRNAs were located in the granule cell layer of the dentate gyrus and the pyramidal cell layer of all subfields of hippocampus. Dopamine receptors in the hippocampus are thought to be postsynaptic, based on immunocytochemical and autoradiographic evidence (Scatton et al., 1980; Swanson, 1982; Goldsmith and Joyce, 1994), so we are detecting the transcripts encoding postsynaptic receptors. MK-801 regulated dopamine receptor gene expression in a dose-dependent, anatomically distinct, and receptor-specific manner.

3.1. D_1 receptor mRNA

MK-801 caused a decrease in dopamine D_1 receptor mRNA in dentate gyrus ($F(3,31) = 7.23$, $P < 0.001$), the only region of the hippocampal formation in which dopamine D_1 receptor mRNA was visualized (Fig. 2). Post-hoc analysis revealed that the lowest dose (0.3 mg/kg) caused a significant decrease in dopamine D_1 receptor mRNA relative to control animals ($P < 0.005$), but the differences between the controls and the middle and highest dose animals was not significant.

3.2. D_2 receptor mRNA

There was a main effect for dose ($F(3,130) = 17.19$, $P < 0.0001$), and for region ($F(4,130) = 6.59$, $P <$

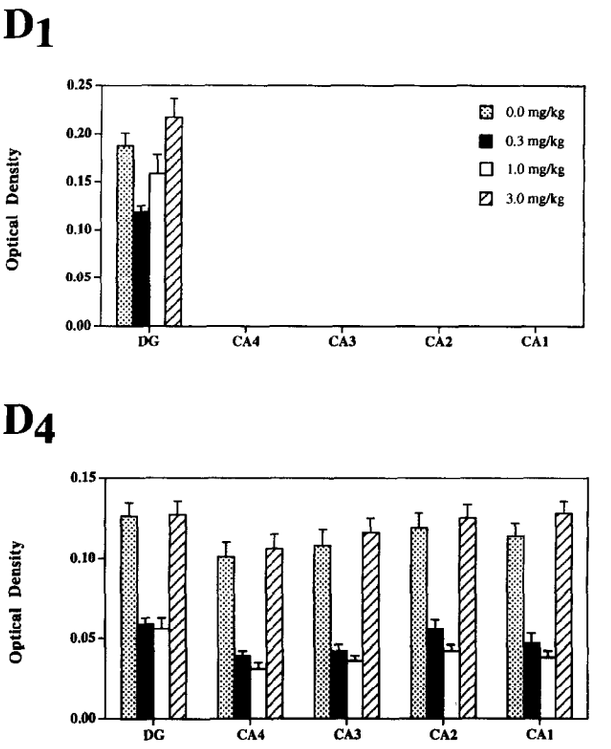

Fig. 2. D_1 and D_4 receptor gene expression, expressed as optical density, in the hippocampal formation after treatment with MK-801. MK-801 had the effect of decreasing the expression of these transcripts at several of the doses used in this study. D_1 was visualized only in the dentate gyrus; MK-801 significantly decreased the expression of D_1 mRNA at 0.3 mg/kg, but not at the other two higher doses. MK-801 treatment significantly decreased the expression of D_4 mRNA at 0.3 and 1.0 mg/kg, but not at the highest dose.

0.0001), but no dose x region interaction ($F(12,130) = 0.47$, P = n.s.) (Fig. 3). Post-hoc analysis revealed that the lowest dose (0.3 mg/kg) and middle dose (1.0 mg/kg) caused a significant increase in dopamine D_2 receptor mRNA relative to control animals ($P < 0.0001$ for both), but the values from the animals treated with the highest dose were not significantly different from control animals. Post-hoc analysis of regional variability of this transcript revealed that the main effect for region was due to the values in the dentate gyrus being greater than those in both CA1 ($P < 0.001$) and CA4 ($P < 0.0001$).

3.3. D_3 receptor mRNA

There was a main effect for dose ($F(3,150) = 21.88$, $P < 0.0001$) and for region ($F(4,150) = 2.49$, $P < 0.05$), but no interaction between dose and region ($F(12,150) = 0.18$, P = n.s.) (Fig. 3). Post-hoc analysis revealed that the middle dose (1.0 mg/kg) caused a significant increase in dopamine D_3 receptor mRNA relative to control animals ($P < 0.0001$), but the values for the animals treated with the lowest and highest doses were not significantly different from control animals. Post-hoc analysis of regional

variability of this transcript revealed that the main effect for region was due to the values in the dentate gyrus being greater than those in CA4 ($P < 0.005$).

3.4. D_4 receptor mRNA

As in the case of dopamine D_2 and D_3 receptors, for D_4 mRNA there was a main effect for dose ($F(3,160) = 169.28$, $P < 0.0001$), and for region ($F(4,160) = 5.49$, $P < 0.0005$), but no interaction between dose and region ($F(12,160) = 0.26$, P = n.s.) (Fig. 2). In this case, however, D_4 mRNA was downregulated, compared to the upregulation of D_2 and D_3. Post-hoc analysis revealed that this downregulation was significant for both the lowest dose ($P < 0.0001$) and middle dose ($P < 0.0001$) groups, but not for the highest dose. Post-hoc analysis of regional variability of this transcript revealed that the main effect for region was due to the values in the dentate gyrus being greater than those in both CA3 ($P < 0.005$) and CA4 ($P < 0.0001$) and CA2 being greater than CA4 ($P < 0.005$).

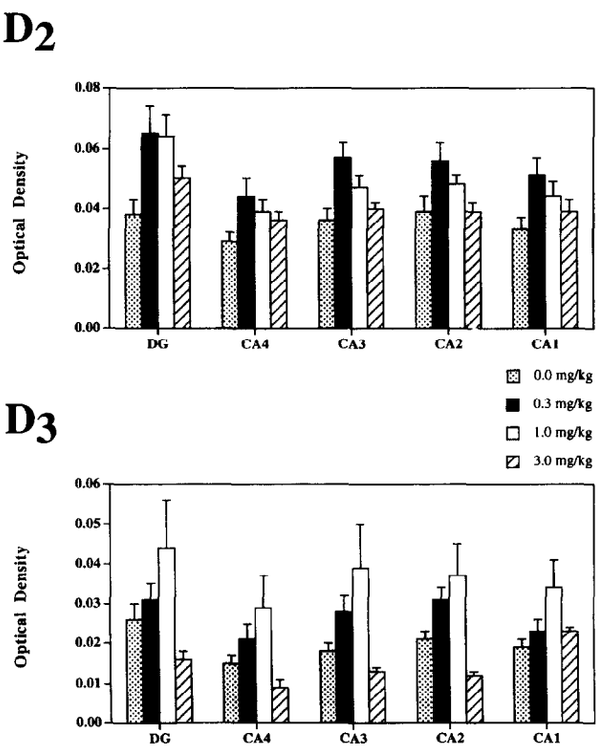

Fig. 3. D_2 and D_3 receptor mRNA expression, expressed as optical density, in the hippocampal formation after treatment with MK-801. MK-801 generally increased expression of these two transcripts at the lower doses used in this study, opposite of what was observed for D_1 and D_4 receptor mRNA. MK-801 significantly increased the expression of D_2 mRNA at 0.3 and 1.0 mg/kg, but not at the highest dose, and significantly increased D_3 mRNA levels at 1.0 mg/kg, but not at the other two doses.

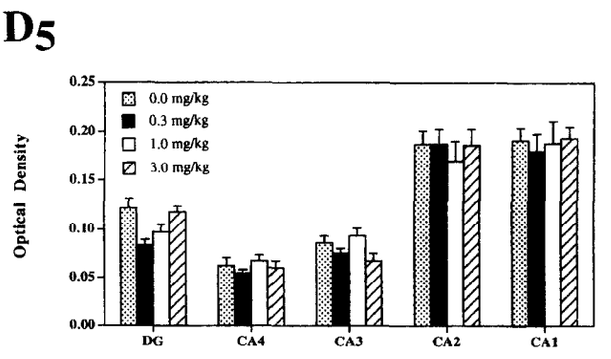

Fig. 4. D_5 receptor expression, expressed as optical density, in the hippocampal formation after treatment with MK-801. This transcript was not altered by MK-801 treatment at any dose.

3.5. D_5 receptor mRNA

There was a main effect for region ($F(4,160) = 96.84$, $P < 0.0001$), but unlike the other four transcripts, there was no main effect for dose ($F(4,160) = 1.26$, P = n.s.) (Fig. 4). There was no dose × region interaction ($F(12,160) = 0.73$, P = n.s.). Post-hoc analysis revealed considerable heterogeneity in the distribution of this transcript, with CA1 and CA2 both greater than CA3, CA4, and dentate gyrus (all $P < 0.0001$), and dentate gyrus greater than both CA3 ($P < 0.005$) and CA4 ($P < 0.0001$).

4. Discussion

The regulation of hippocampal dopamine receptor mRNA by the noncompetitive NMDA receptor antagonist MK-801 displays three distinct patterns.

1. Both dopamine D_1 and D_4 receptor mRNA decreased with the lowest dose, but were not changed by the highest dose treatment. Middle dose caused a decrease in D_4 transcript only.
2. On the other hand, dopamine D_2 and D_3 receptor mRNA both increased with middle dose MK-801 treatment, changing in an opposite, complementary manner to D_1 and D_4 transcripts. As seen with D_1 and D_4 mRNA, however, the highest dose MK-801 did not change D_2 nor D_3 receptor gene expression.
3. Dopamine D_5 receptor gene expression was not regulated by MK-801.

There have been few in vivo studies of the interaction of glutamate and dopamine in the rat hippocampus (Whitton et al., 1994, 1992; Smialowski, 1990). NMDA has been demonstrated to decrease dopamine release in the hippocampus, while the competitive glutamate antagonist D-2-amino-5-phosphonoproprionic acid (D-AP5) had no effect (Whitton et al., 1994). The non-competitive glutamate antagonist MK-801 causes an increase in extracellular dopamine and the dopamine metabolite HVA in hippocampus (Whitton et al., 1992). To our knowledge the present

study is the first to study the effect of MK-801 treatment on dopamine receptor gene expression in the hippocampal formation. The decrease in D_1 and D_4 mRNA we found with MK-801 treatment is consistent with an increase in extracellular dopamine, in turn, leading to a downregulation of postsynaptic dopamine receptors.

The increases that we observed for dopamine D_2 and D_3 receptor mRNA are more difficult to explain. The changes in these two receptor mRNAs might be expected to parallel the changes that we observed for D_1 and D_4 mRNA levels, considering dopamine is the endogenous ligand for all four. One speculative explanation is that there are two populations of cells in the hippocampal formation with dopamine D_1 and D_4 receptors colocalized in one pool and D_2 and D_3 receptors in another. The observed D_1/D_4 effect would be a direct effect of MK-801 on dopamine release, with subsequent receptor down-regulation, while the D_2/D_3 effect would be mediated through an alternate pathway. This functional parcelization might theoretically be similar to the compartmentalization of outflow found in the striatum (Gerfen, 1992), but much research remains to confirm this model. It is also surprising that neither members of the dopamine D_1-like nor D_2-like receptor families were regulated in similar ways. For example, since these families are distinguished by their pharmacological profiles, we expected dopamine D_1 and D_5 receptors to be regulated similarly. Further, it might also be expected that the dopamine D_2-like receptors (D_2, D_3, and D_4) might be similarly regulated. That this was not the case suggests that glutamate regulates dopamine gene expression via complex pathways.

The U shape of the dose-response curve for D_1–D_4 also implies a more complex regulation of gene expression in this experimental paradigm. Intravenous MK-801, at doses greater than 0.1 mg/kg, differentially alters burst firing in neurons in subdivisions of the VTA that project to either the striatum or the frontal cortex, possibly altering dopamine release (Murase et al., 1993). Our highest dose of MK-801 may unmask this phenomenon, and counteract the other mechanism(s) that may be mediating the regulation of dopamine receptor gene expression at lower doses. Additionally, MK-801 has been demonstrated to have micromolar affinity for the dopamine transporter (Clarke and Reuben, 1995), so perhaps the highest dose of MK-801 that we used may show a blunting of the effects observed when using lower doses due to this mechanism. Another possibility is that the lack of a change in D_1–D_4 mRNA may represent a toxic effect of the highest dose of MK-801 treatment on the projections connecting the nucleus accumbens and the hippocampus. The loss of hippocampal-accumbens projections may remove some modulation of the ventral tegmental area projections to the hippocampal formation (Goldsmith and Joyce, 1994), altering the effect of the highest dose of MK-801 on dopamine receptor gene expression. This possibility is supported by the observation that only high dose MK-801 affects D_1–D_3 mRNA levels in the nucleus accumbens (Healy and Meador-Woodruff, 1996).

These data demonstrate that the regulation of dopamine receptor gene expression by an NMDA antagonist in the hippocampal formation is mediated by a complex mechanism, and may be a model to examine the interaction of glutamate and dopamine in this important structure. Converging lines of evidence suggest that this interaction of glutamate and dopamine in the hippocampus may be of some relevance to the pathogenesis of schizophrenia. Several groups (Kovelman and Scheibel, 1984; Bogerts et al., 1985; Altschuler et al., 1990; Benes et al., 1991; Kerwin and Murray, 1992; Akbarian et al., 1993; Squires et al., 1993) have demonstrated the possible involvement of the hippocampal formation in schizophrenia. Theories of schizophrenia have included a functional role for the hippocampus in the generation of psychotic symptoms (Weinberger, 1987; Kerwin and Murray, 1992; Krieckhaus et al., 1992). Krieckhaus et al. (1992) have suggested that CA1 hyperactivity may be a cause for some of the positive symptoms of schizophrenia, and D_2 antagonists decrease hippocampal neuronal firing, thereby ameliorating the symptoms. Deakin et al. (1989), Carlsson and Carlsson (1990), Kerwin et al. (1990), Harrison et al. (1991), Sherman et al. (1991), and Ishimaru et al. (1994) have postulated aberrant glutamate function, particularly in the temporal lobe, as a possible mechanism for schizophrenia. Our data begin to provide evidence linking these lines of evidence by demonstrating that glutamatergic antagonism can cause changes in dopamine receptor gene expression in the hippocampal formation.

Acknowledgements

Dr. Healy was supported by an NIMH Training Grant (MH15794). Dr. Meador-Woodruff was supported by grants from NIMH (MH00818 and MH53327). Additional support was provided by the Department of Psychiatry and the Mental Health Research Institute at the University of Michigan. This paper was selected as one of the winners of the 1996 American Psychiatric Association/Lilly Resident Research Award.

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