ELSEVIER

European Journal of Pharmacology 407 (2000) 131–138

ejp

www.elsevier.nl/locate/ejphar

Activation of the retrohippocampal region in the rat causes dopamine release in the nucleus accumbens: disruption by fornix section

Stephen N. Mitchell [a,*], Ben K. Yee [b], Joram Feldon [c], Jeffrey A. Gray [a], J. Nick P. Rawlins [b]

[a] *Department of Psychology, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK*
[b] *Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford OX1 3UD, UK*
[c] *Behav. Biol. Lab., Swiss Federal Institute of Technology, Schorenstrasse 16, CH8603 Schwerzenbach, Switzerland*

Received 13 September 2000; accepted 20 September 2000

Abstract

There is a well-described projection from the retrohippocampus (subiculum and entorhinal cortex) to the nucleus accumbens that is involved in the control of psychomotor behaviour, and is implicated in the aetiology of schizophrenia. Cortical abnormalities are widely reported in the brains of schizophrenic patients, but it is unclear whether they are the cause or consequence of those changes in subcortical systems that are treated with neuroleptic drugs. We have, therefore, conducted a series of microdialysis experiments in anaesthetized rats to determine whether infusion of the excitotoxin, *N*-methyl-D-aspartate, into the retrohippocampus increases mesolimbic dopamine release. We found a clear and reproducible increase in extracellular dopamine in the nucleus accumbens following *N*-methyl-D-aspartate (2.5 μg), that was abolished when we sectioned the fimbria-fornix. Furthermore, inhibition of γ-aminobutyric acid receptors following retrohippocampus administration of bicuculline (4 μg), also increased dopamine in the nucleus accumbens. The dopamine response to bicuculline was accompanied by an increase in dopamine metabolism, was long lasting, and also reduced by fornix section.

The response to both *N*-methyl-D-aspartate and bicuculline depends on the integrity of the projection from the retrohippocampus to the nucleus accumbens. The results provide an underlying mechanism whereby a primary insult in the temporal cortex, caused by excessive *N*-methyl-D-aspartate receptor stimulation, can produce a hyperdopaminergic state. In addition, an increase in subiculo-accumbens activity evoked by bicuculline may also explain why patients with limbic epilepsy can develop a psychosis.

Keywords: Dopamine; Subiculum; Nucleus accumbens; Fimbria-fornix; Microdialysis; (Rat)

1. Introduction

There is a well-described projection from the ventral subiculum and entorhinal cortex (referred to here as the retrohippocampus) to the nucleus accumbens (Groenewegen et al., 1987; Kelley and Domesick, 1982; Krayniak et al., 1981; Lopes da Silva et al., 1984; Totterdell and Smith, 1986). The projection fibres, which terminate predominantly in the shell region, are in close apposition to dopaminergic afferents arising from the A10 group of ventral tegmentum, and make postsynaptic contact with γ-aminobutyric acid (GABA) containing spiny neurones which also receive dopaminergic projections from the A10 (Sesack and Pickel, 1990b; Totterdell and Smith, 1989). It has been shown that microinjection of *N*-methyl-D-aspartate (NMDA) into ventral subiculum/hippocampal area causes increased locomotor activity (Yang and Mogenson, 1987) and disruption of sensory motor gating (Pouzet et al., 1999). Moreover, the behavioural effects represented an apparent interaction with the mesolimbic dopamine system, as they were influenced by local (nucleus accumbens) stimulation of presynaptic autoreceptors (Yang and Mogenson, 1987), or systemic administration of atypical neuroleptics (Pouzet et al., 1999).

In humans, the ventral hippocampus, including the septo-hippocampal and subiculo-accumbens projection have been implicated in the aetiology of schizophrenia (Gray et al., 1991). Friston et al. (1992) observed an apparent relationship between regional cerebral bloodflow abnormalities and the presence of schizophrenic symptoms in a group of chronic patients. They observed that these

* Corresponding author. Present address: Eli Lilly and Company, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, UK. Tel.: +44-1276-853238; fax: +44-1276-853525.
E-mail address: mitchell_stephen@lilly.com (S.N. Mitchell).

0014-2999/00/$ - see front matter
PII: S0014-2999(00)00741-X

patients showed increased perfusion of the left parahippocampal region that was related to the severity of their condition, regardless of the particular behavioural subsyndrome. Numerous magnetic resonance imaging studies have also shown bilateral reduction in hippocampal formation volume in schizophrenics (Bogerts et al., 1990; Weinberger, 1999). Friston et al. could not distinguish between cause and effect in accounting for the changes in temporal cortical bloodflow that they observed. On the one hand, this increase might be itself a secondary phenomenon; on the other, it is possible the changes in temporal cortex might be primary, and might themselves result in consequent changes in mesolimbic dopamine function (Bogerts et al., 1990; Gray et al., 1991).

The present experiment directly assessed the possibility that potentially pathological hyperactivity in the retrohippocampus might produce dopamine hyperactivity in the mesolimbic system. First, we measured extracellular levels of dopamine in the nucleus accumbens while infusing NMDA into the retrohippocampus. Second, we examined the possibility that section of the fibre projection that runs via the fimbria-fornix from the retrohippocampus to nucleus accumbens would eliminate any response that the infusion might provoke, as would be expected if the response depended upon this direct projection. The control exerted by the retrohippocampus on the nucleus accumbens was further characterised by studying the effect of intra-retrohippocampus injection of bicuculline, a $GABA_A$ receptor antagonist. Inhibition of GABA in limbic areas is associated with seizure activity. Human patients with limbic epilepsy can develop a psychosis, and in animal models for epileptogenesis and schizophrenia, recent occurrence of seizures compromised sensory motor gating in a way compatible with psychotic states in humans (Koch and Ebert, 1998). A second series of experiments were therefore designed to explore the consequent effect of the retrohippocampus administration of bicuculline on levels of dopamine in the nucleus accumbens, as a neurochemical marker for subiculo-accumbens activity.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (290–320 g, Bantin and Kingman Universal) used in these experiments were housed on a 10/14-h dark/light cycle; food and water were available ad libitum.

2.2. Dialysis probe preparation and surgical implantation

Concentric dialysis probes (made using AN69 Hospal membrane, 2 mm in length; o.d. 290 μm when wet) were implanted into the left nucleus accumbens (Louilot and Le Moal, 1994) under chloral hydrate anaesthesia (600 mg/kg i.p.) in a Kopf stereotaxic frame (lambda and bregma in same horizontal plane; measurements from bregma and dura: caudal +1.6 mm, lateral −0.9 mm, vertical −7.3 mm; Paxinos and Watson, 1986). The probes were continuously perfused at 1.5 μl/min (Harvard 22 infusion pump) with Krebs' solution containing (in mM) NaCl (120), KCl (3.8), KH_2PO_4 (1.2), $CaCl_2$ (2.2), $MgSO_4$ (1.2) and glucose (10). Maintenance doses of anaesthetic were administered when required (60–90 mg/h); animals were placed on a heated pad (Vetko, Harvard) and body temperature was maintained between 35–37°C. After 2.5 h of probe implantation, samples were collected every 15 min in tubes containing 1 M glacial acetic acid (1 μl) and immediately assayed using high-performance liquid chromatography (HPLC) with electrochemical detection. Samples were collected for 2 h before a 33-gauge cannula loaded with drug was implanted into the retrohippocampus (co-ordinates from bregma and dura surface: caudal −6.6–7.3 mm, lateral −4.5 mm, vertical −5.5–6.0 mm). After 30 min, the drug was delivered in 1 μl (over 1 min) and the response recorded (i.e. 5 h after implantation of dialysis probe). In some experiments a second administration of drug was made 2 h after the first. The cannula was left in situ for the duration of the experiment.

Within the same dialysis sample, levels of dopamine, and the metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were measured. The limit of detection was 5–10 fmol/sample (10–20 fmol for HVA). Basal levels (fmol/sample ± S.E.M.) were: dopamine 36.4 ± 3.1; DOPAC 6667.1 ± 465.9; HVA 3567.9 ± 246.6 (n = 42).

Under these experimental conditions, removal of Ca^{2+} perfusing the nucleus accumbens 5 h post-implantation, reduced extracellular levels of dopamine to 15.7 ± 1.7% of control values within 45 min. Extracellular levels of DOPAC and HVA were also reduced to 58.3 ± 1.2% and 64.8 ± 7.3%, respectively, within 60 min.

2.3. Fimbria-fornix section

Transection of the fimbria-fornix was accomplished with a custom-made cutter previously described by Feldon et al. (1985). The device consisted of a pair of forceps held horizontally with the tip's 1.5 mm apart. It was inserted at the outset, prior to implantation of the dialysis probe, through the side of the head, at the following co-ordinates: caudal −1.8 mm, lateral −4.5 mm, vertical −5.3 mm. The fimbria-fornix was cut by clamping the forceps together using a screw; they were held shut for 5 min and then opened. The device was left in place for the duration of the experiment.

2.4. Histology

Following the experiment, verification of probe and cannula placements were conducted by perfusion of ink,

either through the probe for 5 min, or by injection of 0.2 μl through the cannula. Brains were fixed in formal-saline then examined, using either 1.0–1.5 mm or 30-μm coronal sections. Examination of fimbria-fornix lesions was also conducted using 1.0–1.5 mm or 30-μm sections.

2.5. HPLC details

The HPLC system consisted of an ACS 351 series pump (HPLC Technology), on-line degasser (ERC 3510, Erma), Chromspher C18 cartridge column (5-μm particle size), guard column and saturation pre-column (all from Chrompack U.K.). Electrochemical detection was accomplished with a LC-4C detector (BAS); working electrode maintained at +0.73 V with respect to an Ag/AgCl reference electrode. Chromatographic separation and electrochemical detection were performed at room temperature. The mobile phase consisted of a 0.1 M citrate/0.2 M phosphate buffer containing 1.4 mM octane sulphonic acid, 7% methanol and 1 mM ethylenediaminetetraacetic acid (final pH 2.75); the flow-rate was 0.75 ml/min. Peaks were displayed, integrated and stored using a Shimadzu C-R3A coupled to an FDD-1A disk drive (Dyson Instruments).

2.6. Materials

All chemicals for HPLC were Analar or HPLC grade (BDH). NMDA and (−)-bicuculline were obtained from Sigma, and MK-801 from Merck, Sharp and Dohme. Drugs were dissolved in 0.1 M phosphate-buffered saline (PBS) at pH 7.4.

2.7. Statistical analysis

The data were expressed as a percentage of a pre-injection control, obtained by averaging the last three samples prior to cannula placement or fimbria-fornix cut (routinely, samples 6–8; equivalent to 100%). Differences in the (maximal) response to the first and second challenge with NMDA in animals with or without transection of the fimbria-fornix, were analysed by analysis of variance (ANOVA) using log-transformed data, followed by post-hoc *t*-tests for individual comparisons. Differences in the response to intra-retrohippocampus administration of bicuculline were analysed by ANOVA with repeated measures using log-transformed data over the whole time period post drug administration.

3. Results

3.1. NMDA administration into the retrohippocampal region on dopamine release and metabolism in the nucleus accumbens: effect of fimbria-fornix transection

In control animals, administration of 2.5 μg NMDA in 1 μl produced a rapid increase in extracellular levels of dopamine, reaching a peak within the first 15 min sample (to 225.9 ± 29.8% relative to pre-injection control period; mean ± S.E.M., $n = 9$). The response was relatively short-lived, returning close to basal levels within the next sample (Fig. 1). A second administration of NMDA (2.5 μg) 2 h after the first produced a comparable increase in extracellular levels of dopamine (to 252.8 ± 38.8%) which failed to differ significantly from the first response (ANOVA for NMDA responses in control group and fimbria-fornix 'cut' group: $F(3,30) = 7.35$, $P < 0.0008$; post-hoc *t*-test for first versus second NMDA challenge in control animals, $P < 0.62$). Vehicle administration (0.1 M PBS, 1 μl) failed to increase levels of dopamine, and extracellular levels of DOPAC or HVA were largely unaffected by either injection of NMDA (figure not shown).

To see whether the induced response in the nucleus accumbens was dependent upon the integrity of the projection from the retrohippocampus, the effects of NMDA were compared in a second group of animals before and after cutting the fimbria-fornix. With the cutting device in position, the first administration of NMDA (2.5 μg in 1 μl) increased extracellular levels of dopamine to 237.5 ± 41.8% ($n = 8$). In these animals, the response to the first challenge with NMDA failed to differ significantly from that obtained in control animals (post-hoc *t*-test, $P < 0.86$). After 60 min, the lesion (obtained by closure of the cutting device for 5 min) the response to a second administration of NMDA was significantly reduced (113.7 ± 14.4%; post-hoc *t*-test: $P < 0.0008$ compared to the first challenge and

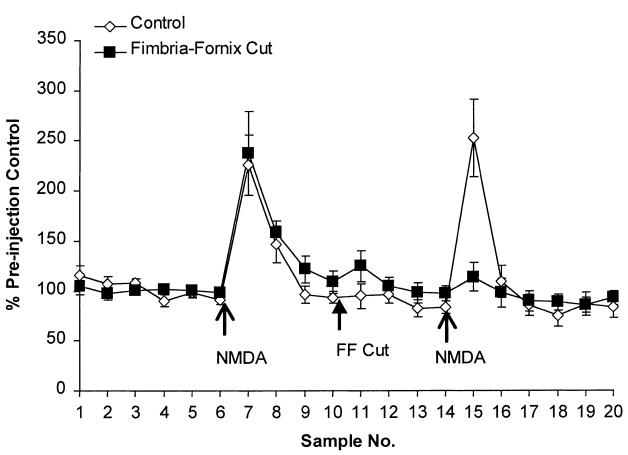

Fig. 1. Effect of NMDA (2.5 μg in 1 μl) administered into the retrohippocampus on extracellular levels of dopamine in the nucleus accumbens in control (normal) animals (open diamonds) and in animals subjected to a fimbria-fornix cut (FF-cut) between successive stimulations with NMDA (full squares). For animals receiving an FF-cut, the cutting device was positioned at the beginning of the experiment just prior to implantation of the dialysis probe. The device was clamped shut for 5 min 1 h prior to the second administration of NMDA. Both the cutting device and injection cannula was left in place for the duration of experiment. NMDA reproducibly increased extracellular levels of dopamine, an effect that was prevented by sectioning the fimbria-fornix. Data expressed as a percentage of a pre-injection control period (mean ± S.E.M.); samples collected every 15 min.

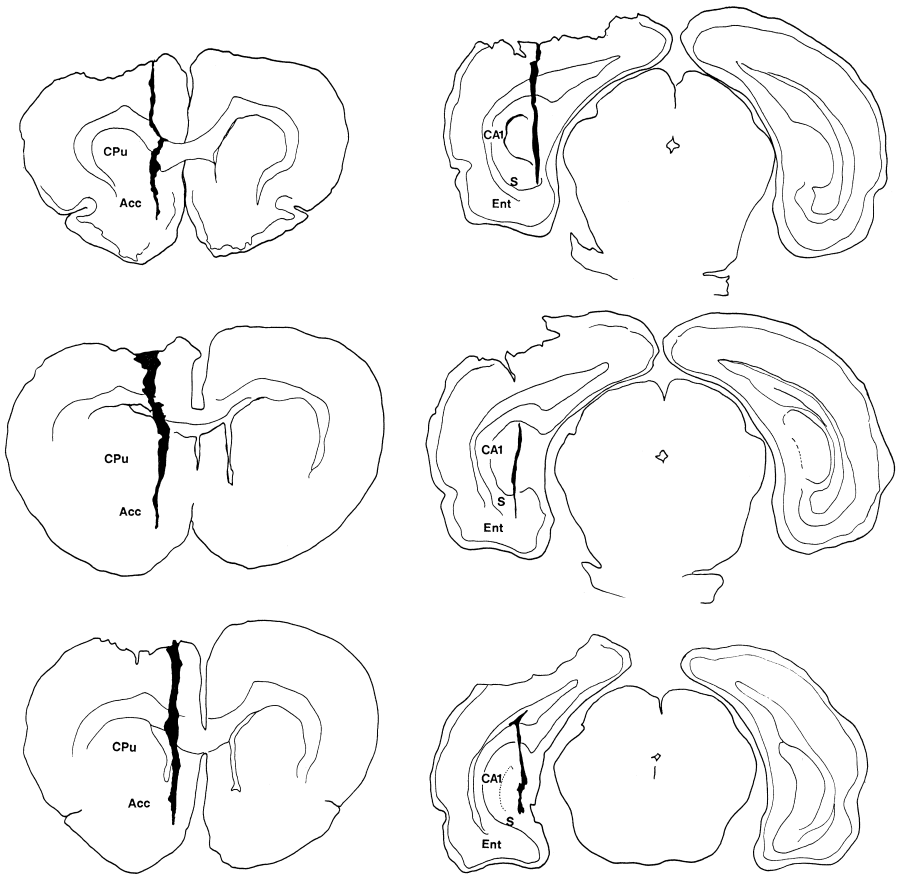

Fig. 2. Outline drawings of coronal sections of rat brain, made using a drawing tube, from three representative subjects showing position of the microdialysis probe placement in the nucleus accumbens and injection cannula in the retrohippocampus. Darkened area shows cannula/probe tract (CPu = caudate putamen; Acc = nucleus accumbens; CA1 = field CA1 of Ammon's horn; S = subiculum; Ent = entorhinal cortex).

$P < 0.0003$ compared to the second challenge in control animals). Fig. 2 shows the position of the injection needle in the retrohippocampus and the microdialysis probe in the contralateral nucleus accumbens (shell) in representative animals, and Fig. 3, an example of the damage following transection of the fimbria-fornix.

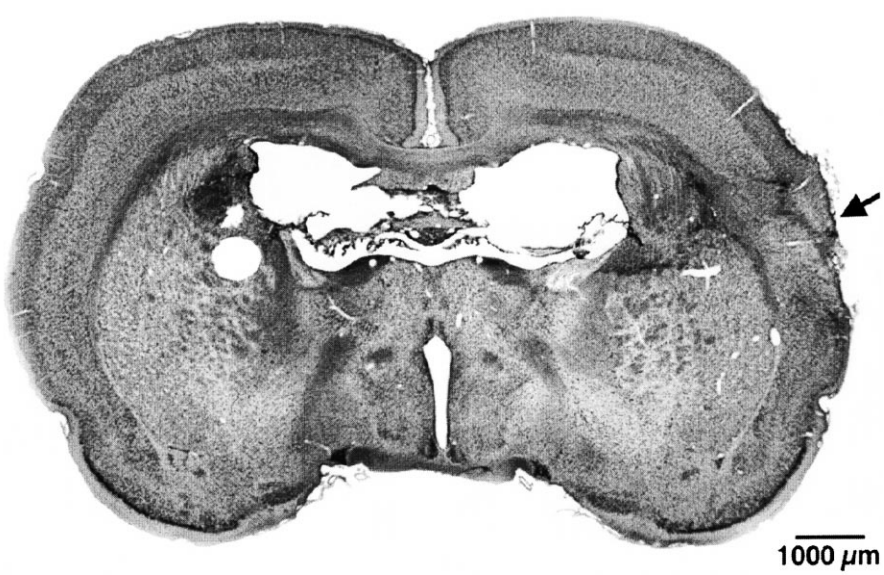

Fig. 3. Photomicrograph of a representative cresyl violet stained section of a brain with fimbria-fornix lesion, at the level where the forceps were inserted (arrow).

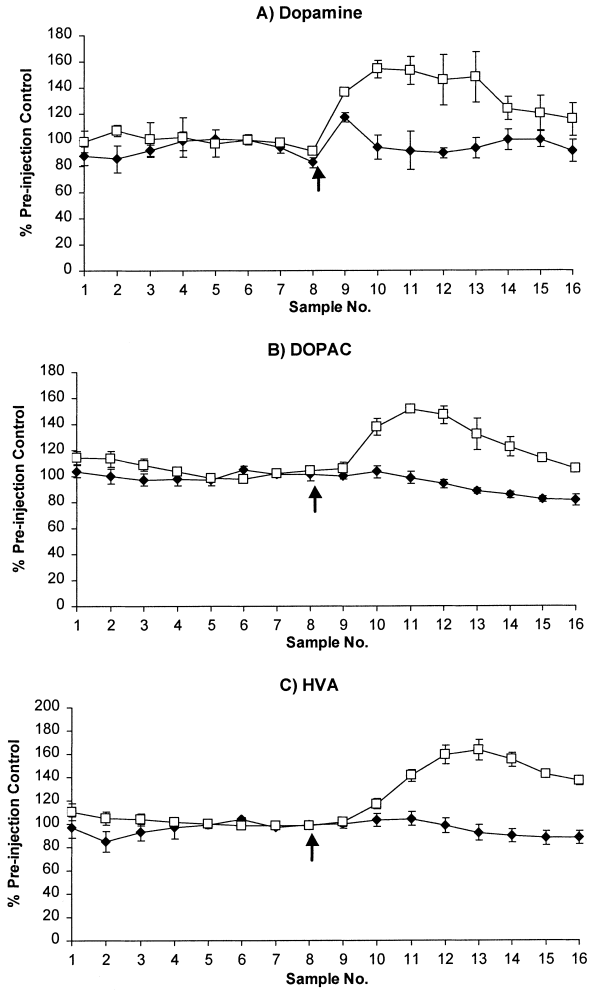

Fig. 4. Administration of bicuculline (♦ = 0.4 μg, □ = 4 μg) into the retrohippocampus and its effects on extracellular levels of dopamine (A) and the metabolites DOPAC (B) and HVA (C) in the nucleus accumbens. Data expressed as a percentage of a pre-injection control period (mean ± S.E.M.); samples collected every 15 min. Bicuculline at 4 μg (in 1 μl, given at arrow), produced a significantly greater increase in extracellular levels of dopamine, DOPAC and HVA than the lower 0.4 μg dose.

The response evoked by administration of NMDA into the retrohippocampus was also Ca^{2+}-dependent. Removal of Ca^{2+} from the Krebs' solution perfusing the nucleus accumbens 1 h after the response to the first administration of NMDA, reduced basal levels to 35.6 ± 5.0% of control, and prevented the effect of the second NMDA administration. The level of dopamine in response to NMDA after Ca^{2+} removal remained at 48.1 ± 13.0% of control ($n = 3$).

3.2. Effect of bicuculline administration into the retrohippocampal region on dopamine release and metabolism in the nucleus accumbens

Intra-retrohippocampus administration of bicuculline at 4 μg increased extracellular levels of dopamine in the nucleus accumbens to a significantly greater extent than that achieved with 0.4 μg (Fig. 4A; main effect: dose, $F(1,9) = 30.43$, $P < 0.001$, $n = 5$). The response obtained with 4 μg bicuculline was more long lasting than seen previously with NMDA, with levels of dopamine being elevated for the duration of recording period. In contrast to the effect of NMDA, bicuculline at 4 μg also increased extracellular levels of DOPAC and HVA, and the response was significantly greater than that produced with the lower dose (Fig. 4B) (main effect: dose, $F(1,9) = 18.80$, $P <$

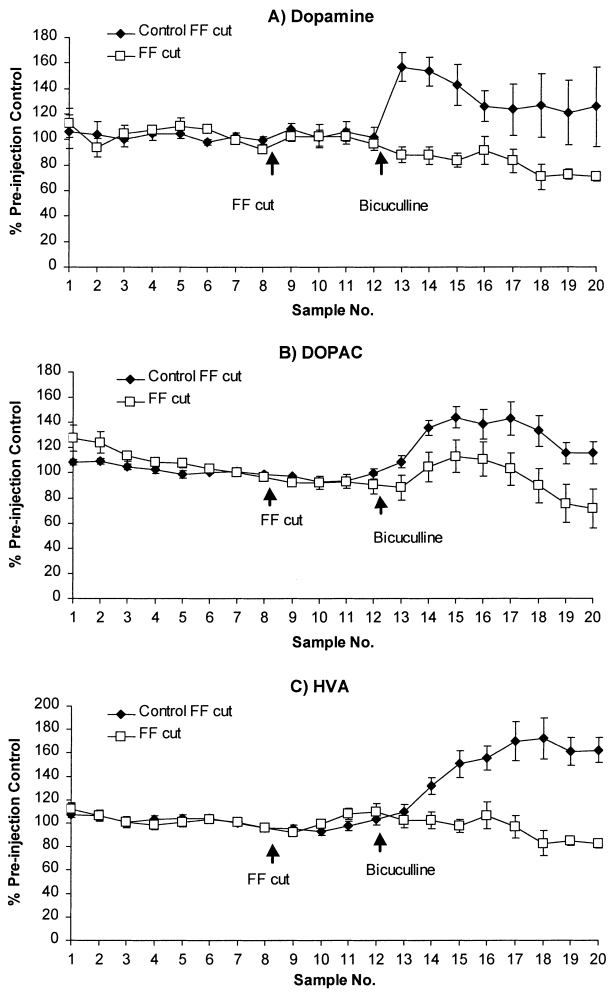

Fig. 5. Effect of a fimbria-fornix transection on the nucleus accumbens response to intra-retrohippocampus administration of bicuculline. In all animals, the cutting device was positioned just prior to implantation of the dialysis probe, and the cannula implanted into the retrohippocampus 30 min prior to drug delivery. In control animals, the cutting device was implanted but not clamped shut; in fornix sectioned animals, the forcep arms were clamped together for 5 min (FF cut); the device was removed at the end of the experiment. Bicuculline (4 μg in 1 μl) was delivered at arrow. Data expressed as a percentage of a pre-injection control period (mean ± S.E.M.); samples collected every 15 min. As seen following NMDA stimulation of the retrohippocampus (Fig. 1), the effect of bicuculline on extracellular levels of dopamine (A), as well as DOPAC (B) and HVA (C), in the nucleus accumbens were inhibited by transection of the fimbria-fornix.

0.01) and HVA (Fig. 4C) (main effect: dose, $F(1,9) = 40.90$, $P < 0.001$).

In order to ascertain whether the response evoked by bicuculline was also dependent upon the integrity of the projection from the retrohippocampus to the nucleus accumbens, an additional experiment was performed in which the response to bicuculline was determined in animals with and without a fimbria-fornix lesion. In these experiments, sectioning the fimbria-fornix prior to administration of bicuculline, significantly attenuated the dopamine response (Fig. 5A: main effect: group, $F(1,11) = 9.93$, $P < 0.01$; $n = 6$ with lesion, $n = 7$ without lesion, but with cutting device in position). The lesion also reduced both the DOPAC (Fig. 5B) and the HVA (Fig. 5C) response to bicuculline (DOPAC, main effect: group, $F(1,11) = 4.93$, $P < 0.05$; HVA, main effect: group, $F(1,11) = 10.56$, $P < 0.01$).

Since bicuculline has been reported to act as an NMDA receptor antagonist at high doses (Krebs et al., 1994), the effect of NMDA receptor inhibition was investigated using dizocilpine (MK-801). However, intra-retrohippocampus administration of MK-801 (0.34 and 3.4 μg; $n = 2–5$), failed to produce any significant alteration in extracellular levels of dopamine, or in the metabolites DOPAC and HVA in the nucleus accumbens.

4. Discussion

The present study indicates that administration of the excitatory amino acid, NMDA, or the $GABA_A$ receptor antagonist, bicuculline, into the ventral subiculum/entorhinal cortex (retrohippocampus) increases dopamine release in the nucleus accumbens. The dopamine response to bicuculline was also accompanied by an increase in dopamine metabolism, as evidenced by an increase in extracellular levels of DOPAC and HVA. Furthermore, the responses to both NMDA and bicuculline depend on the integrity of the fimbria-fornix since they are abolished by transection of this fibre bundle. This is consistent with the possibility that the responses are mediated by the projection from the retrohippocampus to the nucleus accumbens, which courses through the fimbria-fornix.

Neuroanatomical studies have revealed that the nucleus accumbens receives projections from virtually all limbic structures including the hippocampus, amygdala and temporal cortex (Kelley and Domesick, 1982; Kelley et al., 1982; Groenewegen et al., 1987) and that these projections appear to be glutamatergic (Christie et al., 1987; DeFrance et al., 1980; Fuller et al., 1987). Behavioural studies have indicated that the hippocampus and nucleus accumbens, in particular, are functionally related, and support neuroanatomical data implying a specific interaction between glutamatergic and dopaminergic systems. For example, increases in locomotor activity following hippocampal administration of carbachol were blocked by intra-accumbens administration of glutamate antagonists (Mogenson and Nielsen, 1984a,b), while increases in locomotor activity induced by microinjections of NMDA into ventral subiculum were blocked by intra-accumbens administration of the dopamine D_2 autoreceptor agonist, quinperole (Yang and Mogenson, 1987), implying that the behavioural response was a consequence of elevated levels of dopamine. More recently, microdialysis studies have been used to monitor transmitter release directly, and have also shown an increase in extracellular levels of dopamine in the nucleus accumbens following ventral hippocampal/subiculum administration of NMDA (Brudzynski and Gibson, 1997; Legault and Wise, 1999), while immunocytochemical studies have shown an increase in c-Fos protein in the nucleus accumbens and medial prefrontal cortex (Klarner et al., 1998). The experiments reported here also show a functional link between the hippocampus and nucleus accumbens, as measured by microdialysis, and extend those reported previously by showing that the response measured, either with NMDA or bicuculline, is dependent upon an intact fimbria-fornix. Interestingly, Legault and Wise (1999) argued that elevations in nucleus accumbens dopamine following intra-subiculum administration of NMDA may occur from trans-synaptic activation of dopamine cell bodies in the ventral tegmental area, as extracellular levels of dopamine are also elevated in this brain area. The present results showing the dependency of NMDA-evoked dopamine release in the nucleus accumbens on an intact fimbria-fornix may argue against a direct involvement of the ventral tegmental area in the measured response, but do not exclude the possibility of an indirect effect. Indeed, there is no morphological data to support the existence of a projection directly from the ventral subiculum to the ventral tegmental area. Instead, enhanced somatodendritic activity may result from modulation of outputs from the ventral pallidum following activation of the nucleus accumbens (Yang and Mogenson, 1987), or following activation of the prefrontal cortex neurones which also project to the ventral tegmental area (Jay and Witter, 1991; Laroche et al., 1990). In a more recent report, Legault et al. (2000) have shown that the increase in dopamine release in the nucleus accumbens following ventral subiculum administration of NMDA is abolished by local application of the glutamate receptor antagonist, kynurenic acid, in the ventral tegmental area, but not in the nucleus accumbens. Moreover, the evoked response in the nucleus accumbens was dependent on increased impulse flow in the ventral tegmental area—being abolished by the local application of tetrodotoxin. These results identify the ventral tegmental area as a critical site for activation of the nucleus accumbens following subicular injection of NMDA, although the precise neurocircuitry for such activation remains to be determined. Based on the dependency of the response to NMDA on an intact fimbria-fornix, and the lack of any direct input to the ventral tregmental area, one possible circuit may include stimulation of the hip-

pocampal projection to the prefrontal cortex (Jay and Witter, 1991) and activation of glutamatergic inputs to the ventral tegmental area (Sesack and Pickel, 1990a).

In the present experiments, intra-retrohippocampus administration of the $GABA_A$ receptor antagonist bicuculline also increased extracellular levels of dopamine, and by implication, increased the output to the nucleus accumbens. In contrast to NMDA, the dopamine response to bicuculline was also accompanied by an increase in dopamine metabolism, as evidenced by an increase in extracellular levels of DOPAC and HVA. Moreover, increasing the excitability of the retrohippocampus by inhibition of $GABA_A$ receptors produced a more long-lasting increase in dopamine release (and metabolism), and the response was also dependent on the integrity of the fimbria-fornix.

Although a fornix section was successful in abolishing the effects of retrohippocampus activation induced by either NMDA or bicuculline, the inability of the lesion to alter basal levels of dopamine would seem to suggest that under normal conditions the retrohippocampus has little tonic control over dopaminergic function. Although acute deafferentation was without immediate effect on basal release, there is evidence for changes occurring over several weeks following intervention of the hipocampal projection. Interestingly, lesions of the hippocampus have been reported to evoke neurochemical and behavioural sequelae associated with an *increase* in dopaminergic function: increased basal dopamine turnover (determined ex vivo; Lipska et al., 1992, abolition of latent inhibition (LI) Feldon and Weiner, 1992; Weiner, 1990), and increased amphetamine-induced locomotor activity and dopamine release in the nucleus accumbens (Wilkinson et al., 1993).

Gray et al. (1991) proposed that disruption of the input to the nucleus accumbens from the hippocampus may be a primary phenomenon in the aetiology of schizophrenia. Friston et al. (1992) have reported that schizophrenic patients showed increased bloodflow in the parahippocampal region that was related to the severity of their condition. Furthermore, magnetic resonance imaging studies have revealed a reduced volume in this brain area in first episode schizophrenics (Bogerts et al., 1990). It is therefore conceivable that increases in temporal cerebral bloodflow may result in consequent changes in mesolimbic dopamine function (Bogerts et al., 1990; Gray et al., 1991). The findings of the present study, showing that (acute) activation of the retrohippocampus leads directly to enhanced dopamine release in the nucleus accumbens, suggests that a potentially pathological hyperactivity in retrohippocampus might produce schizophrenic symptoms. Moreover, prolonged overactivity through excessive stimulation of NMDA receptors may lead to cell death and degeneration of the hippocampal projection, and in a manner that is seen experimentally in hippocampal-lesioned animals, produce a chronic hyperdopaminergic state. In addition, the over excitation of neurones in the retrohippocampus evoked by bicuculline may parallel the epileptic seizure activity seen in temporal lobe epilepsy, and by producing an increase in dopamine release and metabolism in the nucleus accumbens, suggest how patients with such a condition may also experience psychotic symptoms (Hyde and Weinberger, 1997).

The relevance of retrohippocampus hyperactivity to schizophrenia, or schizophrenic symptoms, has also been shown in animals using pre-pulse inhibition. The disruption of pre-pulse inhibition is commonly used as a model for the sensorimotor gating deficits that are supposed to be the cause of some schizophrenic symptoms. In this paradigm, local intra-subiculum administration of NMDA in rats disrupted pre-pulse inhibition (Wan et al., 1996; Klarner et al., 1998; Pouzet et al., 1999). Interestingly, disruption of pre-pulse inhibition under these conditions could also be reversed by pre-treatment with atypical (Pouzet et al., 1999), but not typical neuroleptics (Wan et al., 1996; Pouzet et al., 1999).

In conclusion, we have shown that administration of the excitatory amino acid, NMDA, or the $GABA_A$ receptor antagonist, bicuculline, into the retrohippocampus increases dopamine release in the nucleus accumbens. These responses are abolished by transection of the fimbria-fornix, suggesting that they were mediated by activation of a projection from the retrohippocampus to the nucleus accumbens, although the precise neurocircuitry remains to be determined. In view of the proposed role of this projection system in the aetiology of schizophrenia (Gray et al., 1991), these findings indicate how changes in the activity of the retrohippocampus may produce schizophrenic symptoms.

Acknowledgements

The work was supported by a grant from Bristol Myers Squibb.

References

Bogerts, B., Ashtariet, M., Degreef, G., Alvir, J., Ma, J., Bilder, R.M., Lieberman, J.A., 1990. Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. Psychiatry Res.: Neuroimaging 35, 1–13.

Brudzynski, S.M., Gibson, C.J., 1997. Release of dopamine in the nucleus accumbens caused by stimulation of the subiculum in freely moving rats. Brain Res. Bull. 42, 303–308.

Christie, M.J, Summers, R.J., Stephenson, J.A., Cook, C.J., Beart, P.M., 1987. Excitatory amino acid projections to the nucleus accumbens septi in the rat: a retrograde transport study utilizing D[^{3}H]aspartate and [^{3}H]GABA. Neuroscience 22, 425–439.

DeFrance, J.F., Marchand, J.E., Stanley, J.C., Sikes, R.W., Chronister, R.B., 1980. Convergence of excitatory amygdaloid and hippocampal input in the nucleus accumbens septi. Brain Res. 185, 183–186.

Feldon, J., Weiner, I., 1992. From an animal model of an attentional deficit towards new insights into the pathophysiology of schizophrenia. J. Psychiatr. Res. 26, 345–366.

Feldon, J., Rawlins, J.N.P., Gray, J.A., 1985. Fornix-fimbria section and the partial reinforcement extinction effect. Exp. Brain Res. 58, 435–439.

Friston, K.J., Liddle, P.F., Frith, C.D., Hirsch, S.R., Frackowiak, R.S.J., 1992. The left medial temporal region and schizophrenia. Brain 115, 367–382.

Fuller, T.A., Russchen, F.T., Price, J.L., 1987. Sources of presumptive glutamatergic/aspartergic afferents to the rat ventral striatopallidal region. J. Comp. Neurol. 258, 317–338.

Gray, J.A., Feldon, J., Rawlins, J.N.P., Hemsley, D.R., Smith, A.D., 1991. The neuropsychology of schizophrenia. Behav. Brain Sci. 14, 1–84.

Groenewegen, H.J., Vermeulen-Van Der Zee, E., Kortschot, A., Witter, M.P., 1987. Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of *Phaseolus Vulgaris* leucoagglutinin. Neuroscience 23, 103–120.

Hyde, T.M., Weinberger, D.R., 1997. Seizures and schizophrenia. Schizophr. Bull. 23, 611–622.

Jay, T.M., Witter, M.P., 1991. Distribution of hippocampal CA1 and subicular afferents in the prefrontal cortex of the rat studied by means of anterograde transport of *Phaseolus vulgaris*-leucoagglutinin. J. Comp. Neurol. 313, 574–586.

Kelley, A.E., Domesick, V.B., 1982. The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: an anterograde- and retrograde-horseradish peroxidase study. Neuroscience 7, 2321–2335.

Kelley, A.E., Domesick, V.B., Nuta, W.J.H., 1982. The amygdalostriatal projection in the rat—an anatomical study by anterograde and retrograde tracing methods. Neuroscience 7, 615–630.

Klarner, A.E., Koch, M., Schnitzler, H.-U., 1998. Induction of Fos-protein in the forebrain and disruption of sensorimotor gating following *N*-methyl-D-aspartate infusion into the ventral hippocampus of the rat. Neuroscience 84, 443–452.

Koch, M., Ebert, U., 1998. Deficient sensorimotor gating following seizures in amygdala-kindled rats. Biol. Psychiatry 44, 290–297.

Krayniak, P.J., Meibach, R.C., Siegel, A., 1981. A projection from the entorhinal cortex to the nucleus accumbens in the rat. Brain Res. 209, 427–431.

Krebs, M.-O., Kemel, M.-L., Gauchy, C., Desban, M., Glowinski, J., 1994. Does bicuculline antagonize NMDA receptors? Further evidence in the rat striatum. Brain Res. 634, 345–348.

Laroche, S., Jay, T.M., Thierry, A.M., 1990. Long-term potentiation in the prefrontal cortex following stimulation of the hippocampal CA1/subicular region. Neurosci. Lett. 114, 184–190.

Legault, M., Wise, R.A., 1999. Injections of *N*-methyl-D-aspartate into the ventral hippocampus increase extracellular dopamine in the ventral tegmental area and nucleus accumbens. Synapse 31, 241–249.

Legault, M., Rompré, P.-P., Wise, R.A., 2000. Chemical stimulation of the ventral hippocampus elevates nucleus accumbens dopamine by activating dopaminergic neurons of the ventral tegmental area. J. Neurosci. 20, 1635–1642.

Lipska, B.K., Jaswik, G.E., Chrapusta, S., Karoum, F., Weinberger, D.R., 1992. Ibotenic acid lesions of the ventral hippocampus differentially affects dopamine and its metabolites in the nucleus accumbens and prefrontal cortex in the rat. Brain Res. 585, 1–6.

Lopes da Silva, F.H., Arnolds, D.E.A.T., Neijt, H.C., 1984. A functional link between the limbic cortex and ventral striatum: physiology of the subiculum–accumbens pathway. Exp. Brain. Res. 55, 205–214.

Louilot, A., Le Moal, M., 1994. Lateralized interdependence between limbicotemporal and ventrostriatal dopaminergic transmission. Neuroscience 59, 495–500.

Mogenson, G.J., Nielsen, M., 1984a. A study of the contribution of hippocampal–accumbens–subpallidal projections to locomotor activity. Behav. Neural Biol. 42, 38–51.

Mogenson, G.J., Nielsen, M., 1984b. Pharmacological evidence that the nucleus accumbens and subpallidal region contribute to exploratory locomotion. Behav. Neural Biol. 42, 52–60.

Paxinos, G., Watson, C., 1986. The Rat Brain in Stereotaxic Coordinates. Academic Press, Sydney.

Pouzet, B., Zhang, W., Weiner, I., Feldon, J., 1999. Atypical but not typical antipsychotics antagonise prepulse inhibition induced by *N*-methyl-D-aspartate infusion in the ventral hippocampus. J. Psychopharmacol. 13, A54.

Sesack, S.R., Pickel, V.M., 1990a. Prefrontal cortical efferents in the rat synapse on unlabelled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. Brain Res. 506, 166–168.

Sesack, S.R., Pickel, V.M., 1990b. In the rat nucleus accumbens, hippocampal and catecholaminergic terminals converge on spiny neurons and are in opposition to each other. Brain Res. 527, 266–279.

Totterdell, S., Smith, A.D., 1986. Cholecystokinin-immunoreactive boutons in synaptic contact with hippocampal pyramidal neurons that project to the nucleus accumbens. Neuroscience 19, 181–192.

Totterdell, S., Smith, A.D., 1989. Convergence of hippocampal and dopaminergic input onto identified neurons in the nucleus accumbens of the rat. J. Chem. Neuroanat. 2, 285–298.

Wan, F.-J., Caine, S.B., Swerdlow, N.R., 1996. The ventral subiculum modulation of prepulse inhibition is not mediated via dopamine D2 or nucleus accumbens non-NMDA glutamate receptor activity. Eur. J. Pharmacol. 314, 9–18.

Weinberger, D.R., 1999. Cell biology of the hippocampal formation in schizophrenia. Biol. Psychiatry 45, 395–402.

Weiner, I., 1990. Neural substrates of latent inhibition: the switching model. Psychol. Bull. 108, 442–461.

Wilkinson, L.S., Mittleman, G., Torres, E., Humby, T., Hall, F.S., Robbins, T.W., 1993. Enhancement of amphetamine-induced locomotor activity and dopamine release in nucleus accumbens following excitotoxic lesions of the hippocampus. Behav. Brain Res. 55, 143–150.

Yang, C.R., Mogenson, G.J., 1987. Hippocampal signal transmission to the pedunculopontine nucleus and its regulation by dopamine D_2 receptors in the nucleus accumbens: an electrophysiological and behavioural study. Neuroscience 23, 1041–1055.