Psychopharmacology (●) : 1–7
DOI 10.1007/s00213-005-0073-9

ORIGINAL INVESTIGATION

Anja Murschall · Wolfgang Hauber

Effects of a systemic AMPA/KA and NMDA receptor blockade on pavlovian–instrumental transfer

Received: 1 April 2005 / Accepted: 10 May 2005

Abstract *Rationale:* Pavlovian stimuli can markedly elevate instrumental responding directed toward a common reward, an effect known as pavlovian–instrumental transfer (PIT). PIT critically depends on the amygdala and nucleus accumbens (ACB); however, little is known yet about its neurochemical basis. *Objective:* Here we examined the role of ionotropic glutamate receptors in PIT. *Methods:* The effects of a systemic blockade of alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate/kainate (AMPA/KA) and *N*-methyl-D-aspartate (NMDA) receptors on PIT and locomotor activity were investigated in rats. *Results:* The competitive AMPA/KA receptor antagonist 6-cyano-7-nitroquinoxaline-2,3-dione disodium salt (CNQX) (1.5 mg/kg i.p.) did not alter the overall rate of lever pressing and left PIT intact, i.e. presentation of a pavlovian stimulus significantly enhanced instrumental responding. Furthermore, CNQX did not affect horizontal and vertical activity in an open field. The non-competitive NMDA receptor antagonist (+)-5-methyl-10,11-dihydro-5*H*-dibenzo [a,d]cyclohepten-5,10-imine hydrogen maleate (dizocilpine) (0.08 mg/kg i.p.) elevated the overall rate of lever pressing but did not affect PIT. In addition, dizocilpine increased horizontal and decreased vertical activity in an open field. *Conclusions:* Previous studies imply that the training protocol used here induced a general, not outcome-specific, form of PIT which is mediated by the central nucleus of the amygdala (CeN) through modulation of mesoaccumbens dopamine transmission. Thus, we suggest that an AMPA/KA and NMDA receptor blockade did not affect PIT here because the general motivational influence of pavlovian stimuli to induce PIT is conveyed by GABAergic projections from the CeN to midbrain dopaminergic neurons.

A. Murschall · W. Hauber (✉)
Abteilung Tierphysiologie, Biologisches Institut,
Universität Stuttgart,
Pfaffenwaldring 57,
70550 Stuttgart, Germany
e-mail: hauber@bio.uni-stuttgart.de
Tel.: +49-711-6855003
Fax: +49-711-6855090

Keywords Instrumental conditioning · Pavlovian conditioning · Glutamate · AMPA/KA · NMDA · Rat

Introduction

Appetitive pavlovian stimuli can markedly elevate instrumental responding directed toward a common reward, a phenomenon termed pavlovian–instrumental transfer (PIT) (Estes 1948; Lovibond 1983; for review, see Dickinson and Balleine 1994). PIT probably reflects excitatory effects of pavlovian stimuli on instrumental responding, which rely on their general motivational as well as sensory-specific influences (Balleine 1994; Colwill and Motzkin 1994; Dickinson and Dawson 1987). Therefore, general and outcome-specific forms of PIT can be separated experimentally (e.g. Corbit and Balleine 2005).

The amygdala and nucleus accumbens (ACB) are key structures in mediating PIT (Blundell et al. 2001; Corbit and Balleine 2005; Hall et al. 2001; Holland and Gallagher 2003); however, little is known yet about its neurochemical basis. There is consistent evidence for a dopaminergic involvement as systemic administration of dopamine receptor antagonists eliminated (Dickinson et al. 2000), whereas intra-ACB infusion of amphetamine enhanced PIT (Wyvell and Berridge 2000). By contrast, a role of glutamate signalling in PIT has been largely neglected, although likely, for several reasons. For instance, anatomical studies demonstrate massive glutamatergic projections from the basolateral amygdala (BLA) to ACB and midbrain (Wright et al. 1996), i.e. major components of a circuit implicated in conveying pavlovian influences on instrumental responding (Hall et al. 2001). In addition, behavioural studies revealed that *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate/kainate (AMPA/KA) receptors in the ACB play a critical role in speeding instrumental action probably by mediating the invigorating impact of pavlovian stimuli (e.g. Giertler et al. 2003). Therefore, we examined here the effects of a systemic blockade of AMPA/KA and NMDA receptors on PIT.

Materials and methods

Subjects

Subjects were 35 naive male Lister hooded rats (Harlan-Winkelmann, Borchen, Germany) weighing 155–200 g on arrival. Rats were housed in groups of five animals in a temperature-controlled room at 20±2°C on a 12:12-h light–dark cycle (lights on at 7.00 A.M.) with free access to water and standard laboratory maintenance chow (Altromin, Lage, Germany). Before the onset of behavioural training, food was restricted to 15 g per animal per day to maintain ~85% of the animals free-feeding weight. All animal experiments were conducted according to the German law on animal protection and approved by the proper authorities.

Apparatus

Conditioning and testing took place in three identical operant chambers (24×21×30 cm) (Med Associates, St. Albans, VT, USA) housed within sound-attenuating cubicles. Each operant chamber was equipped with a food receptacle, a food dispenser which delivered one pellet (45 mg pellets, Bioserve, Frenchtown, NJ, USA) when activated and a retractable lever on the left side of the food receptacle. Illumination was provided by a 24 V/3 W houselight mounted on the top-centre of the wall opposite the food receptacle. The speaker, which delivered the auditory-conditioned stimuli, was mounted on the wall opposite the lever and the food receptacle. A computer system (MedPC-Software; Med Associates) controlled the equipment and recorded the data.

Locomotor activity was examined in an open field (70×70 cm) divided into nine squares of equal size. The testing area was illuminated by two red light bulbs (20 W), ventilated by a computer fan and surrounded by a cubicle providing optical and acoustical isolation. Horizontal and vertical motor activity was monitored by a video recording system and analysed off-line.

Behavioural procedure

Pavlovian–instrumental transfer

This experiment comprised three main stages: pavlovian training, instrumental training and transfer testing; in this latter stage, the effect of the pavlovian stimuli on instrumental behaviour was analysed in extinction. The behavioural procedure was similar to a protocol by Dickinson et al. (2000). Each session started with the illumination of the houselight and insertion of the lever where appropriate and ended with the retraction of the lever and turning off of the houselight.

Magazine training First, all subjects (N=35) received one session of magazine training to habituate the animals to the operant chambers. During magazine training, food pellets (45 mg pellets, Bioserve) were delivered on a random time (RT) 30-s schedule with no lever available.

Pavlovian training Twelve sessions of pavlovian training were given with the lever retracted. Two 80-dB auditory stimuli (3-kHz tone and white noise) served as CS+ and CS− in a counterbalanced fashion. Each session contained six 2-min presentations of the CS+, followed by an inter-stimulus interval (ISI) of 2–4 min. Reward was delivered only during the presentation of the CS+ on an RT-30-s schedule. For approximately half of the animals the CS+ was the tone, and for the other half the CS+ was the white noise. As a measure of pavlovian conditioning, the total time the animal spend in the food receptacle during CS+ and ISI was recorded via a photobeam in the food receptacle.

Instrumental training Following pavlovian training, all animals received nine instrumental training sessions with the lever inserted. Responding on the lever was reinforced on a random interval (RI) schedule starting with RI-2 s during the first session. For the next two sessions, the schedule was increased to RI-15 and RI-30 s, and, for the remaining six sessions, to RI-60 s. The total numbers of lever presses were recorded and the session ended after 30 min.

Reminder and instrumental extinction Subsequent to instrumental training, one pavlovian reminder was given to habituate unconditioned responses to the CS−. This session was similar to pavlovian training sessions except that two additional, not reinforced, 2-min presentations of the alternative neutral stimuli (CS−) and additional ISI were given preceding the fifth and following the sixth presentation of the CS+. In addition, the animals received a single 30-min instrumental extinction session with the lever available, but not reinforced.

Transfer test The effects of pavlovian stimuli on instrumental behaviour was tested in extinction, whereas the lever was inserted into the operant chamber. Each stimulus (CS+ and CS−) was 2 min in duration and preceded by a 2-min ISI period. The session always started with the presentation of the CS+ and ended after four presentations of each stimulus type (CS+ and CS−). The total numbers of lever presses during the transfer test were recorded separately for CS+, CS− and ISI. Subjects were assigned to three different groups receiving either 6-cyano-7-nitroquinoxaline-2,3-dione disodium salt (CNQX) (n=10), (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (dizocilpine) (n=10) or saline (n=15) before the transfer test.

Open field

Subsequent to pavlovian–instrumental transfer testing, effects of CNQX and dizocilpine on locomotor activity were assessed in a subgroup of rats. Subjects received either injections of dizocilpine (n=14), CNQX (n=8) or saline (n=6) and were placed into the open field for 30 min. The number of line crossings (horizontal activity) and rearings (vertical activity) in six 5-min intervals was counted.

Drugs

CNQX (Sigma, Steinheim, Germany) and dizocilpine (RBI, Natick, MA, USA) were dissolved in physiological saline (0.9%). CNQX (1.5 mg/kg i.p.) and dizocilpine (0.08 mg/kg i.p.) were administered 20 min before the onset of the transfer test and open-field experiment, respectively, in a volume of 1 ml/kg; control subjects received saline (1 ml/kg i.p.) in both experiments.

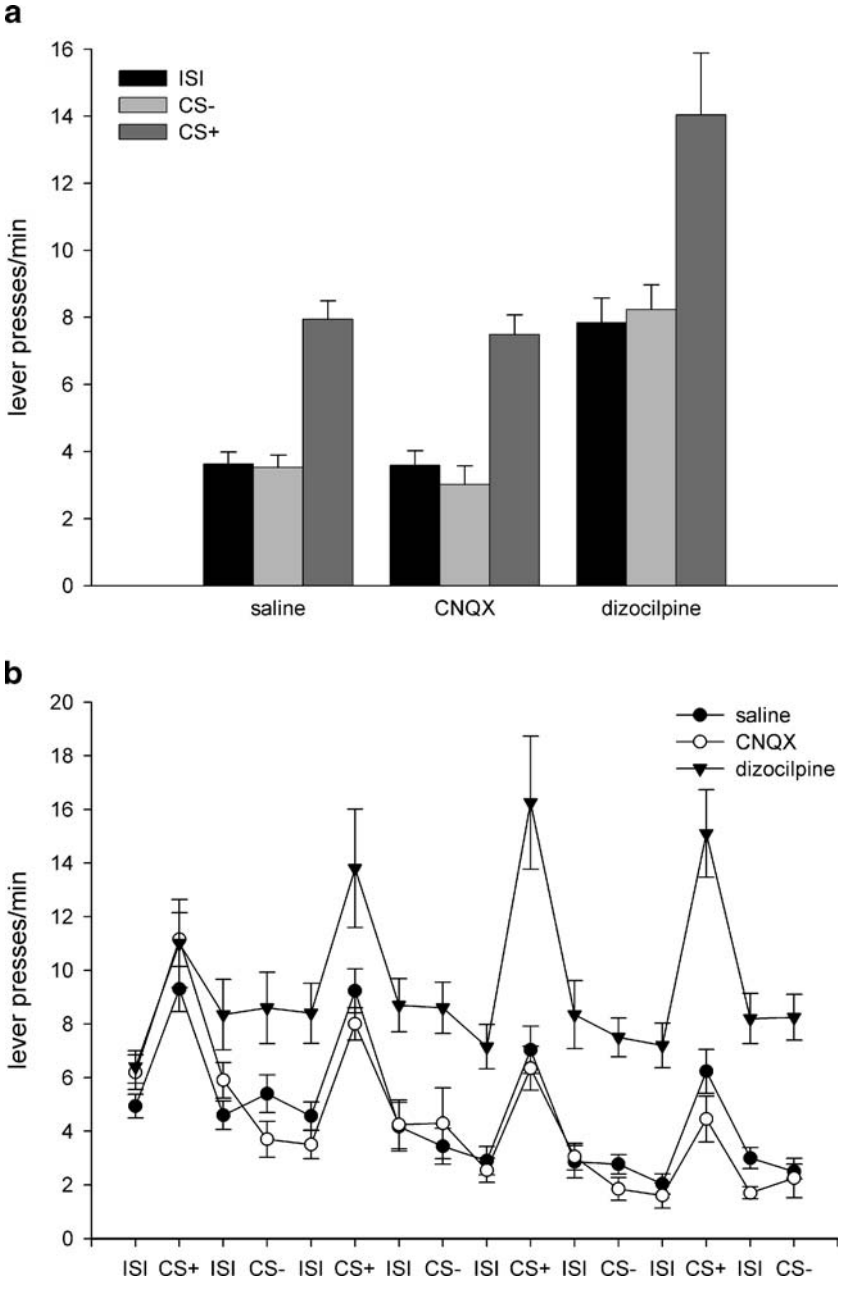

Fig. 1 Pavlovian–instrumental transfer. Systemic administration of CNQX (1.5 mg/kg i.p.) or dizocilpine (0.08 mg/kg i.p.) did not affect pavlovian–instrumental transfer. **a** Overall mean lever presses during the transfer test session. **b** Mean lever presses as a function of the temporal order of stimulus presentation during the transfer test session; *CS+*, conditioned stimulus; *CS−*, neutral stimulus; *ISI*, interstimulus interval (2 min in duration, respectively). The CS+ significantly elevated instrumental responding relative to CS− and ISI in all treatment groups. In dizocilpine-, but not in CNQX-treated subjects, the level of instrumental responding was significantly increased relative to saline-treated subjects

Statistical analysis

Data are presented as means with standard errors of the mean (±SEM). Lever-press rates from pavlovian–instrumental transfer testing were subjected to a two-way analysis of variance (ANOVA) for repeated measures, with drug as between-subjects factor and stimulus as within-subjects factor. Significant main effects were investigated post hoc using the Tukey HSD test. Locomotor activity counts were analysed by an ANOVA for repeated measures, with drug as between-subjects factor and time as within-subjects factor. Significant main effects were investigated post hoc using the Tukey HSD test; significant interactions were further analysed by a test for simple main effects. The level of statistical significance was $p<0.05$. All statistical analyses were carried out using STATISTICA Version 6.1 (StatSoft, Tulsa, OK, USA).

Results

Pavlovian–instrumental transfer

Pavlovian training Stimulus-directed behaviour during pavlovian training over 12 days was measured by calculating the approach ratio, i.e. the percentage of time spent

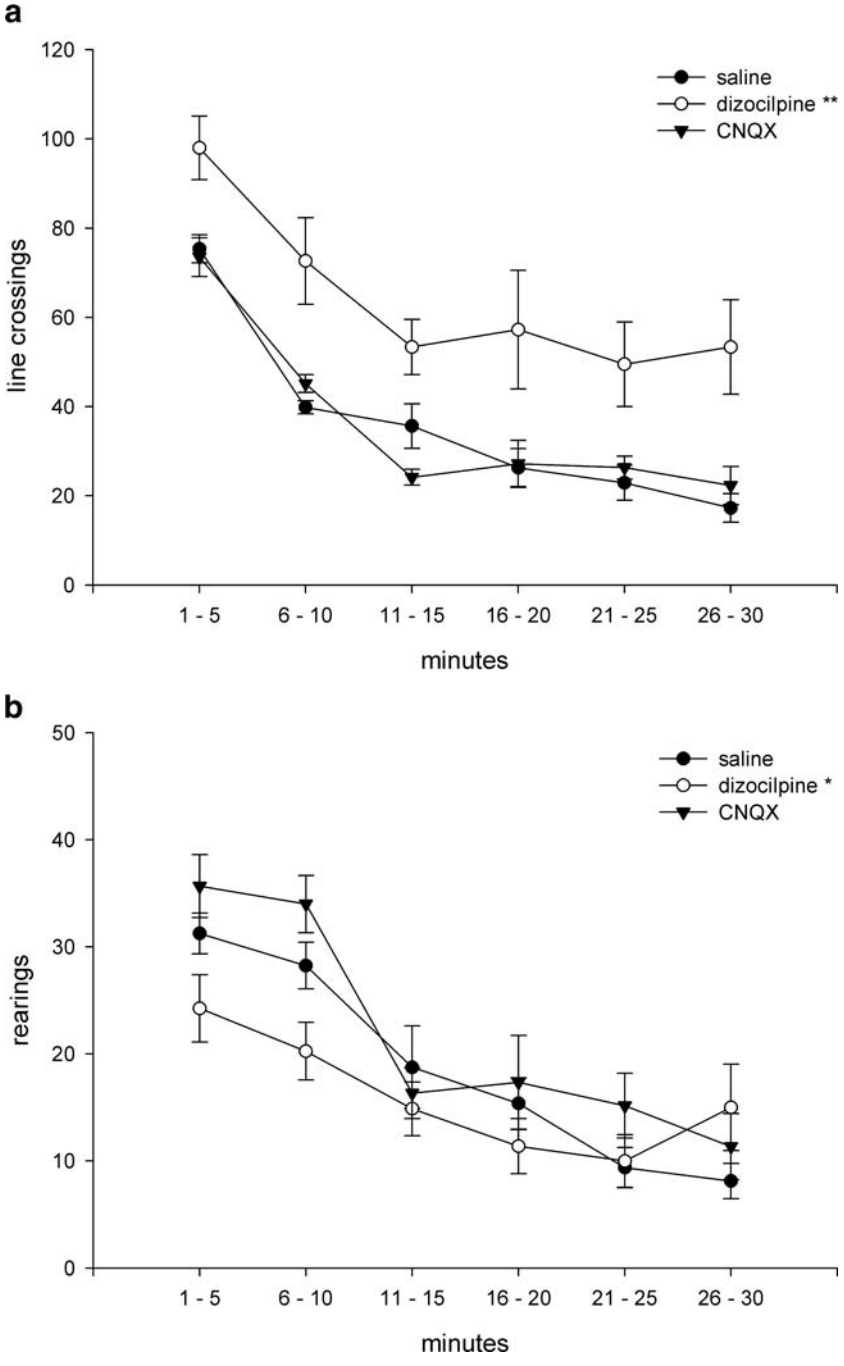

Fig. 2 Effects of systemic administration of CNQX (1.5 mg/kg i.p.), dizocilpine (0.08 mg/kg i.p.) or saline (1 ml/kg i.p.) on locomotor activity in an open field. **a** Horizontal activity measured by the number of line crossing in 5-min intervals (**$p<0.001$, main effect of drug compared to saline treatment). **b** Vertical activity measured by the number of rearings in 5-min intervals (*$p<0.01$, Drug×Time interaction compared to saline treatment). Dizocilpine produced a general increase in horizontal activity and an initial decrease in horizontal activity

in the food receptacle during CS+ and the percentage of time spent in the food receptacle during ISI as follows: approach ratio=(% CS)/(% CS+% ISI) (e.g. Cardinal et al. 2003). The mean approach ratio from all subjects (N=35) was 62±2% on day 1 and 65±2% on day 12.

Instrumental training All animals acquired instrumental responding over 9 days. The number of responses increased from 3.29±0.20 lever presses/min on day 1 to 10.46±0.38 on day 9. In the subsequent extinction session, instrumental responses decreased to 6.30±0.21 lever presses/min.

Transfer test Presentation of the pavlovian stimulus (CS+) increased instrumental behaviour relative to the non-reinforced stimulus (CS−) and ISI, and this effect was evident in all treatment groups (Fig. 1a). The elevation of lever pressing during CS+ compared to CS− and ISI was similar regardless of CS+ identity (tone or white noise) which was used in a counterbalanced way across all treatment groups. A one-way ANOVA indicated that the transfer effect induced by tone vs white noise did not differ significantly [$F_{(1,33)}$=0.028; p=0.96]; therefore, respective data were collapsed. A two-way ANOVA, with drug as between-group factor (three levels: saline, CNQX and dizocilpine) and stimulus as within-subject factor (three levels: CS+, CS− and ISI), revealed a significant main effect of drug [$F_{(2,32)}$=22.79; p<0.001] and a significant main effect of stimulus [$F_{(2,64)}$=86.08; p<0.001], but no drug×stimulus interaction [$F_{(4,64)}$=1.32; p=0.271]. Post hoc analysis on significant main effects indicated that lever presses were significantly higher during presentation of the CS+ as compared with CS− or ISI (p<0.001; Tukey HSD test) in all treatment groups. Furthermore, lever presses were significantly higher after dizocilpine (p<0.001; Tukey HSD test), but not after CNQX, relative to saline.

In addition, a detailed analysis of the time course of effects showed that presentation of the CS+ increased instrumental behaviour throughout the session regardless of the time of presentation and drug treatment (Fig. 1b). A two-way ANOVA, with drug as between-group factor (three levels: saline, CNQX and dizocilpine) and stimulus/time-block as within-subject factor, revealed a significant main effect of drug [$F_{(2,32)}$=23.56; p<0.001], a significant main effect of stimulus/time-block [$F_{(15,480)}$=31.18; p< 0.001] and a significant drug×stimulus/time-block interaction [$F_{(30,480)}$=3.93; p<0.001] (Fig. 1b). Post hoc comparison on significant main effects indicated that lever presses were significantly higher during CS+ relative to CS− and ISI (p<0.001; Tukey HSD test). In addition, lever presses were significantly higher after dizocilpine (p< 0.001; Tukey HSD test), but not after CNQX, compared with saline.

Open field

Horizontal activity ANOVA revealed significant main effects of drug [$F_{(2,25)}$=15.03; p<0.001] and time [$F_{(5,125)}$= 76.25; p<0.001], but no significant drug×time interaction [$F_{(10,125)}$=1.31; n.s.]. Post hoc comparisons on drug effects using the Tukey HSD test further demonstrated a significant effect of dizocilpine, but not of CNQX, compared to saline (Fig. 2a).

Vertical activity ANOVA indicated no significant main effect of drug [$F_{(2,25)}$=2.83; p=0.078], but of time [$F_{(5,125)}$= 40.76; p<0.001]. In addition, there was a significant drug × time interaction [$F_{(10,125)}$=2.68; p<0.01]. Further analysis of simple main effects revealed a significant dose × time interaction between dizocilpine and saline [$F_{(5,100)}$=4.07; p<0.01], but not between CNQX and saline [$F_{(5,90)}$=0.99; n.s.]. Figure 2b shows that the vertical activity was considerably less during the first 10 min in dizocilpine-treated rats compared to saline-treated animals.

Discussion

The results of these experiments demonstrate that a systemic blockade of AMPA/KA and NMDA receptors did not impair PIT, a transfer effect which probably reflects the excitatory impact of pavlovian stimuli on instrumental responding.

Dizocilpine is a selective non-competitive NMDA receptor antagonist which induces prominent motor stimulant effects, e.g. hyperlocomotion and stereotypies (Clineschmidt et al. 1982b; Kloog 1988). The dose used here was shown to produce motor stimulation, but not, as higher doses are used, muscle relaxation and ataxia (e.g. Danysz et al. 1994), which could compromise instrumental action. In keeping with previous findings (Clineschmidt et al. 1982a; Danysz et al. 1994; Loscher and Honack 1992), our present data reveal that systemic administration of dizocilpine at a dose of 0.08 mg/kg i.p. significantly increased horizontal locomotor activity in the open field but had only moderate effects on vertical activity. Thus, the general increase in lever pressing seen here after dizocilpine administration might also rely on motor stimulant actions of a systemic NMDA receptor blockade. By contrast, the competitive AMPA/KA receptor antagonist CNQX (Sheardown 1993) altered neither horizontal and vertical activity in the open field nor the general rate of lever pressing. The lack of motor effects is unlikely to reflect inappropriate dosing. In general, systemic administration of CNQX, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline (NBQX) and other AMPA/KA receptor antagonists did not affect spontaneous motor behaviour (Danysz et al. 1994; Hauber and Andersen 1993; Klockgether et al. 1991) but, for instance, increased motor stimulant effects of L-DOPA (Klockgether et al. 1991). As with dizocilpine, the dose of CNQX used here was shown to induce behavioural effects, but not, as higher doses are used, muscle relaxation, which could interfere with instrumental responding (Backstrom and Hyytia 2003). For instance, systemic administration of CNQX given at the same dose (1.5 mg/kg) and to the same conditions (i.p. administration 20 min before behavioural testing) as here did not alter locomotor activity but attenuated ethanol-seeking behaviour elicited

by ethanol-associated stimuli (Backstrom and Hyytia 2004) and reinstatement of cocaine seeking under a second order schedule (Backstrom and Hyytia 2003). Although reinstatement of cocaine seeking was also attenuated by a higher dose (3 mg/kg), this effect was attributed in part to CNQX-induced motor impairments (Backstrom and Hyytia 2003), an observation which prompted us to use a lower dose (1.5 mg/kg). Given these results, CNQX treatment should be effective in our experiment, although the general rate of lever pressing during PIT and locomotor activity in the open field was not altered.

Notably, CNQX and dizocilpine did not interfere with PIT, suggesting that ionotropic glutamate receptors may not be involved in mediating this transfer effect. Furthermore, these results imply that neither drug produced sensorimotor impairments as the magnitude of PIT was similar across all treatment groups. The finding of intact PIT after ionotropic glutamate receptor blockade was surprising in view of the neural circuits implicated in PIT, which comprise prominent glutamatergic projections. For instance, lesion studies suggest that PIT critically depends on the ACB (de Borchgrave et al. 2002; Hall et al. 2001), a structure with strong glutamatergic input from cortex and BLA (Wright et al. 1996). In addition, lesions of the central nucleus of the amygdala (CeN) reduced PIT, whereas lesions of the BLA had no effect (Hall et al. 2001; Holland and Gallagher 2003). In contrast to these findings, Blundell et al. (2001) reported that BLA, but not CeN lesions, abolished PIT. These apparently discrepant results are likely to be due to different training protocols and forms of PIT used in these experiments. A recent study by Corbit and Balleine (2005) addressing this issue revealed that both BLA and CeN contribute to PIT, but their involvement depends on the form of PIT, i.e. the BLA conveys the outcome-specific form of PIT, whereas the CeN serves the general form of PIT. The general form of PIT is thought to rely on the general motivating effects of an appetitive pavlovian stimulus, i.e. instrumental responding may be enhanced during presentation of an appetitive CS+ as a result of non-specific motivational arousal. The outcome-specific form of PIT refers to another mechanism through which pavlovian CS probably modulates instrumental responding, i.e. an appetitive CS+ may also act selectively to energize an instrumental action—in the presence of other response options—with which it shares the same outcome. In the present as in various other studies (Hall et al. 2001; Holland and Gallagher 2003), a PIT procedure was employed in which rats were trained on a single lever, and the effect of a single pavlovian stimulus on performance of that lever was measured. This protocol generates a form of PIT which relies on the general motivational influence of the pavlovian stimulus and is mediated by the CeN (Corbit and Balleine 2005). Thus, although not explicitly examined, the transfer test used here might involve the general form of PIT mediated by the CeN.

As stimulation of mesoaccumbens dopamine neurotransmission increased PIT (Wyvell and Berridge 2000), the CeN has been suggested to control PIT by modulating the activity of mesoaccumbens dopamine projections (Hall et al. 2001) through efferents to the vicinity of midbrain dopamine neurons (Wallace et al. 1992). Importantly, CeN projections to the midbrain use γ-amino-butyric acid (GABA) as a neurotransmitter (Swanson and Petrovich 1998). Furthermore, the input from the CeN to midbrain dopamine neurons might not be direct but probably involves projections to non-dopamine neurons (Wallace et al. 1992), which in part express GABA receptors (Suaud-Chagny et al. 1992). Accordingly, inactivation of the CeN was associated with decreased basal levels of dopamine efflux in the ACB (Ahn and Phillips 2002). In view of this connectivity, we suggest that an AMPA/KA and NMDA receptor blockade did not affect PIT here, because the general motivational influence of pavlovian stimuli to induce PIT is conveyed by GABAergic projections from the CeN to midbrain dopaminergic neurons. However, a recent study with knock-out mice indicates an involvement of AMPA GluR2 subunits in PIT (Mead and Stephens 2003). However, mutants with a GluR2 deletion show an increased calcium influx, through AMPA receptor-gated ion channels and a facilitated AMPA-dependent long-term potentiation (Jia et al. 1996) and the behavioural effects of these functional AMPA receptor changes are therefore difficult to relate to those of a competitive AMPA receptor blockade used here.

Taken together, our present results demonstrate that a systemic blockade of AMPA/KA and NMDA receptors did not affect PIT. One possibility to explain these findings is that we tested a general form of PIT which critically involves the CeN modulating midbrain mesoaccumbens dopamine neurons by GABAergic projections.

Acknowledgements We thank Prof. A. Dickinson for helpful comments on PIT.

This research was supported by a grant of the Deutsche Forschungsgemeinschaft (DFG Ha2340/6-1).

References

Ahn S, Phillips AG (2002) Modulation by central and basolateral amygdalar nuclei of dopaminergic correlates of feeding to satiety in the rat nucleus accumbens and medial prefrontal cortex. J Neurosci 22:10958–10965

Backstrom P, Hyytia P (2003) Attenuation of cocaine-seeking behaviour by the AMPA/kainate receptor antagonist CNQX in rats. Psychopharmacology (Berl) 166:69–76

Backstrom P, Hyytia P (2004) Ionotropic glutamate receptor antagonists modulate cue-induced reinstatement of ethanol-seeking behavior. Alcohol Clin Exp Res 28:558–565

Balleine B (1994) Asymmetrical interactions between thirst and hunger in pavlovian–instrumental transfer. Q J Exp Psychol B 47:211–231

Blundell P, Hall G, Killcross S (2001) Lesions of the basolateral amygdala disrupt selective aspects of reinforcer representation in rats. J Neurosci 21:9018–9026

Cardinal RN, Parkinson JA, Marbini HD, Toner AJ, Bussey TJ, Robbins TW, Everitt BJ (2003) Role of the anterior cingulate cortex in the control over behavior by pavlovian conditioned stimuli in rats. Behav Neurosci 117:566–587

Clineschmidt BV, Martin GE, Bunting PR, Papp NL (1982a) Central sympathomimetic activity of MK-801, a substance with potent anticonvulsant, central sympathomimetic and apparent anxiolytic properties. Drug Dev Res 2:135

Clineschmidt BV, Martin GE, Bunting PR (1982b) Anticonvulsant activity of (1)-5-methyl-10,11-dihydro-5H-dibenzo[a, d]cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic, and apparent anxiolytic properties. Drug Dev Res 2:123–134

Colwill RM, Motzkin DK (1994) Encoding of the unconditioned stimulus in pavlovian conditioning. Anim Learn Behav 22: 384–394

Corbit LH, Balleine B (2005) Double dissociation of basolateral and central amygdala lesions on the general outcome-specific forms of pavlovian–instrumental transfer. J Neurosci 25:962–970

Danysz W, Essmann U, Bresink I, Wilke R (1994) Glutamate antagonists have different effects on spontaneous locomotor activity in rats. Pharmacol Biochem Behav 48:111–118

de Borchgrave R, Rawlins JN, Dickinson A, Balleine BW (2002) Effects of cytotoxic nucleus accumbens lesions on instrumental conditioning in rats. Exp Brain Res 144:50–68

Dickinson A, Balleine B (1994) Motivational control of goal-directed action. Anim Learn Behav 22:1–18

Dickinson A, Dawson GR (1987) Pavlovian processes in the motivational control of instrumental performance. Q J Exp Psychol 39:201–213

Dickinson A, Smith J, Mirenowicz J (2000) Dissociation of pavlovian and instrumental incentive learning under dopamine antagonists. Behav Neurosci 114:468–483

Estes W (1948) Discriminative conditioning. II. Effects of a pavlovian conditioned stimulus upon a subsequently established operant response. J Exp Psychol 38:173–177

Giertler C, Bohn I, Hauber W (2003) The rat nucleus accumbens is involved in guiding of instrumental responses by stimuli predicting reward magnitude. Eur J Neurosci 18:1993–1996

Hall J, Parkinson JA, Connor TM, Dickinson A, Everitt BJ (2001) Involvement of the central nucleus of the amygdala and nucleus accumbens core in mediating pavlovian influences on instrumental behaviour. Eur J Neurosci 13:1984–1992

Hauber W, Andersen R (1993) The non-NMDA glutamate receptor antagonist GYKI 52466 counteracts locomotor stimulation and anticataleptic activity induced by the NMDA antagonist dizocilpine. Naunyn Schmiedebergs Arch Pharmacol 348:486–490

Holland PC, Gallagher M (2003) Double dissociation of the effects of lesions of basolateral and central amygdala on conditioned stimulus-potentiated feeding and pavlovian–instrumental transfer. Eur J Neurosci 17:1680–1694

Jia Z, Agopyan N, Miu P, Xiong Z, Henderson J, Gerlai R, Taverna FA, Velumian A, MacDonald J, Carlen P, Abramow-Newerly W, Roder J (1996) Enhanced LTP in mice deficient in the AMPA receptor GluR2. Neuron 17:945–956

Klockgether T, Turski L, Honore T, Zhang ZM, Gash DM, Kurlan R, Greenamyre JT (1991) The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys. Ann Neurol 30:717–723

Kloog Y (1988) Mode of binding of [3H]dibenzocycloalkenimine (MK-801) to the N-methyl-D-aspartate (NMDA) receptor and its therapeutic implications. FEBS 230:167–170

Loscher W, Honack D (1992) The behavioural effects of MK-801 in rats: involvement of dopaminergic, serotonergic and noradrenergic systems. Eur J Pharmacol 215:199–208

Lovibond PF (1983) Facilitation of instrumental behavior by a pavlovian appetitive conditioned stimulus. J Exp Psychol Anim Behav Process 9:225–247

Mead AN, Stephens DN (2003) Involvement of AMPA receptor GluR2 subunits in stimulus-reward learning: evidence from glutamate receptor gria2 knock-out mice. J Neurosci 23:9500–9507

Sheardown MJ (1993) The pharmacology of AMPA receptors and their antagonists. Stroke 24:I146–I147 (discussion I153–I154)

Suaud-Chagny MF, Chergui K, Chouvet G, Gonon F (1992) Relationship between dopamine release in the rat nucleus accumbens and the discharge activity of dopaminergic neurons during local in vivo application of amino acids in the ventral tegmental area. Neuroscience 49:63–72

Swanson LW, Petrovich GD (1998) What is the amygdala? Trends Neurosci 21:323–331

Wallace DM, Magnuson DJ, Gray TS (1992) Organization of amygdaloid projections to brainstem dopaminergic, noradrenergic, and adrenergic cell groups in the rat. Brain Res Bull 28:447–454

Wright CI, Beijer AV, Groenewegen HJ (1996) Basal amygdaloid complex afferents to the rat nucleus accumbens are compartmentally organized. J Neurosci 16:1877–1893

Wyvell CL, Berridge KC (2000) Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. J Neurosci 20:8122–8130