Published in final edited form as:

Neurosci Lett. 2012 February 6; 508(2): 106–109. doi:10.1016/j.neulet.2011.12.028.

Cocaine-taking and cocaine-seeking behaviors in rats remain stable after systemic administration of GYKI 52466, a non-competitive AMPA receptor antagonist

Ratika Srivastava, Zheng-Xiong Xi, and Eliot L. Gardner

National Institute on Drug Abuse, Intramural Research Program, Baltimore, MD 21224 USA

Abstract

Given the posited role of enhanced AMPA-mediated synaptic transmission in relapse to drug seeking, we investigated whether the systemic administration of AMPA receptor antagonist GYKI 52466 inhibits cocaine-taking and cocaine-seeking behavior in rats. Rats were trained to self-administer cocaine until stable self-administration was achieved. Effects of GYKI 52466 (1, 3, or 10 mg/kg, i.v.) on cocaine self-administration were assessed. Animals were allowed to reestablish stable cocaine self-administration and were then behaviorally extinguished from drug taking. The effects of GYKI 52466 (3, 10 mg/kg, i.v.) on cocaine-induced reinstatement of drug-seeking behavior were assessed. We found that GYKI 52466 failed to inhibit cocaine-taking and cocaine-seeking in both the self-administration and reinstatement paradigms. We suggest that although AMPA receptors may be involved in cocaine reward and addiction, the AMPA receptor antagonist GYKI 52466 has low therapeutic potential for cocaine addiction treatment.

Keywords

GYKI 52466; AMPA receptor antagonist; cocaine; self-administration; reinstatement

Introduction

Addiction constitutes a maladaptive form of learning [2,6,12]. Glutamate, the major excitatory neurotransmitter in the brain, is posited to play an important role in learning and memory as well as in cocaine-induced neuroplasticity in the mesolimbic dopamine (DA) pathway. Cocaine is a DA transporter inhibitor that causes an increase in extracellular DA by inhibiting DA reuptake [1]. This DA-augmenting action is believed to mediate cocaine-induced reward and relapse to cocaine-seeking behavior [11,24]. In addition, growing evidence has begun to implicate glutamate transmission in reinstatement (relapse) of cocaine-seeking behavior [3,8,10,23]. For example, acute cocaine priming produces a significant increase in extracellular glutamate in the nucleus accumbens (NAc), a critical brain region involved in drug reward and addiction [10,11,12,16,18]. Electrophysiological

Corresponding Authors: Zheng-Xiong Xi: 443-740-2517, zxi@mail.nih.gov. Ratika Srivastava: 443-740-2504, ratika.srivastava@nih.gov.

Author Contributions: R.S. conducted cocaine self-administration and reinstatement experiments, analyzed data and wrote the first draft of the manuscript. Z.-X.X. designed and supervised the experiments, analyzed data and revised the manuscript. E.L.G. supervised the experiments and revised the manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

studies have also shown that cocaine administration caused enhanced glutamate transmission in the ventral tegmental area and the NAc, an effect that is mediated predominantly by up-regulation of AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) glutamate receptor subtype [2]. Consistent with these findings, microinjections of AMPA receptor antagonists into the NAc blocked cocaine-induced reinstatement of drug-seeking behavior [3], suggesting an important role of NAc AMPA receptors in relapse to drug-seeking behavior. Thus, AMPA receptor antagonism has been proposed to be useful in the prevention of relapse [3,11,25]. Indeed, recent studies in medication development for treatment of addiction have converged on drugs that alter glutamate transmission, including AMPA receptors [20,25].

Although several competitive AMPA receptor antagonists (such as DNQX, NBQX, CNQX) have shown some efficacy in animal models of addiction [2,3,5,19,21], they have low application to humans because such compounds also interfere with normal excitatory glutamate transmission and produce unwanted side-effects. Alternatively, much effort has been undertaken to develop non-competitive AMPA receptor antagonists that act at allosteric binding site(s) on the trans-membrane domain of the AMPA receptors. Since non-competitive AMPA antagonists functionally down-regulate (attenuate) excessive glutamate transmission that occurs under various pathological conditions including drug addiction [10], but themselves have no significant effect on normal glutamate transmission, they are believed to cause fewer adverse effects when used in humans [22].

GYKI 52466 and its analogs are non-competitive systemically active AMPA receptor antagonists [4], which are currently under clinical trials for treatment of a variety of neurological disorders including Parkinson's disease, anxiety, and epilepsy [2]. In experimental animals, GYKI 52466 was reported to attenuate expression of cocaine-conditioned locomotion [9]. In the present study, we investigated the effects of GYKI 52466 on cocaine self-administration and cocaine-induced reinstatement of drug-seeking behavior. To the best of our knowledge, such a study has not been previously reported.

Materials and Methods

Animals

Twenty-four male Long-Evans rats from Charles River Laboratories (Raleigh, NC, USA) were used in these experiments. At the start of drug treatment, animals weighed between 350 and 450 g. Rats were individually housed in a climate-controlled colony room and maintained on a reversed light-dark cycle (lights on at 7:00 pm, lights off at 7:00 am) with free access to food and water in their home cages. Experiments were approved by the Animal Care and Use Committee of the National Institute on Drug Abuse of the National Institutes of Health.

Surgical Procedures

Intravenous (i.v.) catheter surgery was performed as previously reported [26]. Rats were anaesthetized using sodium pentobarbital (65 mg/kg intraperitoneal, i.p.). Surgery was performed using standard aseptic surgical techniques. A microrenathane catheter (Braintree Scientific Inc., Braintree, MA, USA) was inserted into the right jugular vein. The distal end of the catheter passed subcutaneously to the top of the skull, where it connected to a modified 24 G cannula (Plastics One, Roanoke, VA, USA) mounted to the skull with dental cement and jewelers' screws. A cannula cap was secured over the head-mounted connector at all times except during experimental sessions, when the connector was attached to the injection pump in the experimental chamber via tubing encased in a protective metal spring.

In order to prevent blockage, catheters were flushed daily with a gentamicin-heparin-saline solution (ICN Biochemicals, Cleveland, OH, USA).

Drugs and Chemicals

Cocaine HCl (Sigma Chemical Co., Saint Louis, MO, USA) was dissolved in physiological saline. GYKI 52466 was obtained from Ascent Scientific Ltd. (Princeton, NJ, USA) and dissolved in saline to prepare dosage solutions of 1, 3 and 10 mg/ml. All doses of GYKI 52466 were administered intravenously (i.v.). Intravenous drug delivery is faster and more efficient in reaching higher blood drug levels and in penetrating the blood-brain barrier than intraperitoneal drug delivery, by which the majority of the drug may be metabolized in the liver (first-pass effects). Thus, we chose i.v. drug administration to determine, in concept, whether or not blockade of brain AMPA receptors by GYKI52466, a systemically-effective AMPA receptor antagonist, inhibits cocaine-taking and cocaine-seeking behavior.

Experiment 1: Cocaine self-administration

After recovery from surgery, each rat was placed in an operant test chamber (32 × 25 × 33 cm) from Med Associates Inc. (Georgia, VT, USA) for i.v. self-administration. Each chamber had two levers, one active and one inactive, located 6.5 cm from the test chamber floor. Active lever presses resulted in an infusion, whereas inactive lever presses were recorded but had no consequence. Each daily session lasted 3 hours, and the house light was kept on for its duration. When the rat pressed the active lever, a cocaine infusion lasting 4.6 s was administered by an infusion pump. During the infusion, the rat was exposed to a cue-light and cue-sound. During the 4.6 s infusion, additional lever presses were counted but did not lead to additional cocaine administrations. To prevent overdose, each rat was limited to a maximum number of 50 cocaine infusions per test session.

For the first 5 days of self-administration training, cocaine was given under a fixed-ratio 1 (FR1) schedule of reinforcement. After 3–5 days of stable responding under high-dose cocaine administration (1 mg/kg per infusion), subjects were switched to a lower dose of cocaine (0.5 mg/kg per infusion) under FR2 reinforcement until stable self-administration was achieved (<10% variability in inter-response interval and <10% variability in number of active lever presses for at least 3 consecutive days). The higher dose was initially used to facilitate acquisition of self-administration; switching to a lower dose facilitated greater reinstatement responding by increasing the number of lever presses [3].

After three or more days of stable responding, each rat randomly received one of 3 doses (1, 3, or 10 mg/kg, i.v.) of GYKI 52466 or vehicle (saline) 10 minutes prior to the start of the self-administration session. After each dose test, subjects were re-trained on cocaine self-administration alone for an additional 7–10 days to re-establish baseline response rates. The order of testing of the various doses of GYKI 52466 was counterbalanced, and effects on cocaine-taking behavior were assessed by comparing the mean number of cocaine infusions per test session. Of the 24 rats that were initially trained, only 8 animals received all four drug doses (including vehicle) due to infection or low catheter patency. Therefore, data from these 8 subjects are analyzed in the present report.

Experiment 2: Extinction training and Cocaine-induced reinstatement

After the completion of Experiment 1, animals were allowed to re-establish stable rates of cocaine self-administration and were then switched to extinction conditions. During extinction, cocaine was replaced with saline and the light and sound cues that previously accompanied infusions were turned off. Rats continued under extinction reinforcement conditions until the number of active lever presses was reduced to <10 times per session for

at least 3 consecutive days. Two doses of GYKI 52466 (3, 10 mg/kg, i.v.) and vehicle were tested on reinstatement of cocaine-seeking behavior.

Eight animals were used in Experiment 2. On the first reinstatement test day, rats were given vehicle (saline) 10 minutes prior to a priming injection of cocaine (10 mg/kg, i.p.), and then were placed into the operant chambers. Extinction conditions continued for at least 5 days before the next reinstatement test. The order of testing of the various doses of GYKI 52466 was counterbalanced. Reinstatement conditions were identical to those in the extinction sessions, i.e., active lever presses were recorded without drug infusions or accompanying cues for 3 hours. Effects of GYKI 52466 on cocaine-induced reinstatement were assessed by comparing the mean number of active lever presses per test session.

Statistical Analysis

Data are presented in figures as means ($\pm$ SEM). The effects of GYKI 52466 on cocaine self-administration and cocaine reinstatement were assessed using one-way analysis of variance (ANOVA). Post-hoc individual group comparisons were examined using the Holm-Sidak multiple comparison procedure ($p < .05$).

Results

Immediately after being given GYKI 52466 at a dose of 10 mg/kg (i.v.), rats displayed a considerable decrease in locomotor activity to the point of temporary paralysis and exhibited strong symptoms of sedation. After a few minutes, the rats began to recover by showing slow and uncoordinated movement. By 10 minutes post-administration, all animals had regained their initial level of alertness and activity. Lower doses (1, 3 mg/kg, i.v.) of GYKI 52466 had no sedative effects.

GYKI 52466 does not inhibit cocaine self-administration

Figure 1 shows infusion data from the 8 subjects that received all 3 doses of GYKI 52466 in addition to vehicle. GYKI 52466 administered 10 minutes before cocaine self-administration sessions neither altered total number of cocaine infusions (Fig. 1, $F_{3,21} = 0.87$, $p = .47$) nor altered the pattern of cocaine self-administration (data not shown). Cocaine-taking behavior in each dose condition was comparable to behavior after saline.

GYKI 52466 does not attenuate cocaine-primed reinstatement of drug-seeking behavior

Figure 2 illustrates total number of lever presses during the last session of self-administration, the last extinction session, and the reinstatement test session for vehicle, 3, or 10 mg/kg GYKI 52466. In the reinstatement tests, a cocaine priming injection (10 mg/kg, i.p.) resulted in increased active lever pressing in the control group as well as in both GYKI 52466 dose groups. Active lever presses during reinstatement were significantly more than those during extinction (Figure 2A; $F_{1,14} = 28.2$, $p = .001$). Using Holm-Sidak pairwise multiple comparisons, we found that cocaine priming produced an increase in active lever pressing in the vehicle group ($t = 3.64$, $p = .002$), the 3 mg/kg GYKI 52466 group ($t = 2.82$, $p = .01$), and the 10 mg/kg GYKI 52466 group ($t = 3.80$, $p = .001$) as compared to each group in the non-primed extinction condition.

Importantly, Figure 2A illustrates that neither 3 mg/kg nor 10 mg/kg of GYKI 52466 altered active lever press responses during reinstatement testing. Active lever pressing in both GYKI 52466 groups was comparable to that seen after vehicle ($F_{2,14} = 0.04$, $p = .96$). Figure 2B shows that GYKI 52466 had no effect on inactive lever pressing ($F_{2,14} = 0.15$, $p = .86$).

Discussion

The present data strongly suggest that the non-competitive AMPA receptor antagonist GYKI 52466 has no effect on either cocaine self-administration or cocaine-triggered relapse to cocaine-seeking behavior in laboratory rats. These findings are congruent with those of Stephens and Brown [21], who found that GYKI 52466 (5 or 10 mg/kg) had no effect on operant ethanol self-administration, but at variance with those of Sanchis-Segura et al. [19], who found that GYKI 52466 (4, 10 mg/kg, i.p.) produced a dose-dependent inhibition of cue-triggered relapse to ethanol-seeking behavior. It is possible that higher doses of GYKI 52466 may alter cocaine taking and cocaine-seeking behavior. However, we observed significant unwanted inhibitory effects on locomotion after administration of the highest dose (10 mg/kg) of GYKI 52466, suggesting that higher doses would be clinically untenable. We should note that the ineffectiveness of GYKI 52466 on cocaine taking under FR2 reinforcement and cocaine seeking during abstinence does not mean that AMPA receptors are not involved in drug reward and addiction. It is possible that GYKI 52466 might alter cocaine taking under progressive-ratio (PR) reinforcement, a more sensitive paradigm to evaluate a drug's rewarding efficacy. However, a positive finding in such a PR self-administration paradigm alone, combined with strong negative findings in classical FR cocaine self-administration and reinstatement paradigms, is insufficient to support the potential use of this compound in the treatment of cocaine addiction.

Many researchers, including ourselves [8,15,16,17,23,25], have proposed that glutamatergic neural mechanisms may at least partially mediate relapse to drug-seeking behavior for a variety of addictive drugs [for reviews, see 1,2,7,12,13,14,25]. Such proposals are congruent with an emerging picture of glutamatergic mechanisms in the mesocorticolimbic system as a crucial substrate for addictive drug reward and relapse – in particular, the role of glutamatergic projections from the prefrontal cortex to the NAc core in cocaine-seeking behavior [3,18]. Though GYKI 52466 did not alter cocaine-seeking behaviors, our other research continues to support the hypothesis that reduction in basal glutamate transmission and enhanced glutamate responding contribute to cocaine-, cue-, or stress-triggered relapse [25].

Schmidt and Pierce [20] used microinjection techniques to show that anatomically-specific blockade of AMPA receptor-mediated signaling in NAc attenuates cocaine-induced reinstatement of drug-seeking behavior [5,18]. Thus, it is possible that if we had used anatomically-specific microinjections of GYKI 52466 into the NAc, we might have observed an inhibitory effect on cocaine-seeking behavior. However, such intracranial drug delivery is impractical in medication development for treatment of drug addiction in humans. As mentioned earlier, another caution is that ataxia, sedation, and temporary paralysis have been observed in rats receiving GYKI 52466 [9,21].

Bowers et al. [2] describe promising results from clinical trials that test AMPA receptor antagonists on neurological conditions such as epilepsy, Parkinson's disease, and neuralgia. However, the present study demonstrated that GYKI 52466 did not reduce cocaine-taking and cocaine-seeking behaviors. These findings likely generalize to structurally-related compounds such as Talampanel and Perampanel that are currently undergoing clinical trials. We suggest that such GYKI analogs, though generally well-tolerated in humans and currently under study for the treatment of other disorders, may not serve to treat drug addiction. Nevertheless, as negative AMPA receptor allosteric modulators constitute a new and relatively novel pharmacological class, more research is needed into a possible role for such compounds in modulating drug-taking and drug-seeking behaviors.

Conclusion

This preclinical animal study used the self-administration and reinstatement paradigms to evaluate the effects of GYKI 52466, a negative allosteric modulator of AMPA receptors, on cocaine taking and relapse to cocaine-seeking behavior. GYKI 52466 failed to alter cocaine self-administration at doses of 1, 3 or 10 mg/kg (i.v.) in laboratory rats and failed to alter cocaine-primed reinstatement of drug-seeking behavior at doses of 3 or 10 mg/kg (i.v.). We conclude that while GYKI 52466 may be useful in treating various other neurological disorders [2], it is less likely to effectively treat cocaine addiction.

Acknowledgments

This research was supported entirely by the Intramural Research Program of the National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services.

References

1. Anderson SM, Pierce RC. Cocaine-induced alterations in dopamine receptor signaling: implications for reinforcement and reinstatement. *Pharmacol Ther.* 2005; 106:389–403. [PubMed: 15922019]
2. Bowers MS, Chen BT, Bonci A. AMPA receptor synaptic plasticity induced by psychostimulants: the past, present, and therapeutic future. *Neuron.* 2010; 67:11–24. [PubMed: 20624588]
3. Cornish JL, Kalivas PW. Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *J Neurosci.* 2000; 20:RC89. [PubMed: 10899176]
4. Donevan SD, Rogawski MA. GYKI 52466, a 2,3-benzodiazepine, is a highly selective, noncompetitive antagonist of AMPA/kainate receptor responses. *Neuron.* 1993; 10:51–9. [PubMed: 7678966]
5. Famous KR, Kumaresan V, Sadri-Vakili G, Schmidt HD, Mierke DF, Cha JH, Pierce RC. Phosphorylation-dependent trafficking of GluR2-containing AMPA receptors in the nucleus accumbens plays a critical role in the reinstatement of cocaine seeking. *J Neurosci.* 2008; 28:11061–70. [PubMed: 18945913]
6. Fuchs RA, Branham RK, See RE. Different neural substrates mediate cocaine seeking after abstinence versus extinction training: a critical role for the dorsolateral caudate-putamen. *J Neurosci.* 2006; 26:3584–8. [PubMed: 16571766]
7. Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. *Biochem Pharmacol.* 2008; 75:218–65. [PubMed: 17706608]
8. Hayes RJ, Vorel SR, Spector JA, Liu X, Gardner EL. Electrical and chemical stimulation of the basolateral complex of the amygdala reinstates cocaine-seeking behavior in the rat. *Psychopharmacology.* 2003; 168:75–83. [PubMed: 12545331]
9. Hotsenpiller G, Giorgetti M, Wolf ME. Alterations in behaviour and glutamate transmission following presentation of stimuli previously associated with cocaine exposure. *Eur J Neurosci.* 2001; 14:1843–55. [PubMed: 11860480]
10. Kalivas PW. Addiction as a pathology in prefrontal cortical regulation of corticostriatal habit circuitry. *Neurotox Res.* 2008; 14:185–9. [PubMed: 19073425]
11. Kalivas PW. Neurobiology of cocaine addiction: implications for new pharmacotherapy. *Am J Addict.* 2007; 16:71–8. [PubMed: 17453607]
12. Kalivas PW. Glutamate systems in cocaine addiction. *Curr Opin Pharmacol.* 2004; 4:23–9. [PubMed: 15018835]
13. Kenny PJ, Markou A. The ups and downs of addiction: role of metabotropic glutamate receptors. *Trends Pharmacol Sci.* 2004; 25:265–72. [PubMed: 15120493]
14. Knackstedt LA, Kalivas PW. Glutamate and reinstatement. *Curr Opin Pharmacol.* 2009; 9:59–64. [PubMed: 19157986]
15. Li X, Gardner EL, Xi Z-X. The metabotropic glutamate receptor 7 (mGluR7) allosteric agonist AMN082 modulates nucleus accumbens GABA and glutamate, but not dopamine, in rats. *Neuropharmacology.* 2008; 54:542–51. [PubMed: 18155073]

16. Li X, Li J, Gardner EL, Xi Z-X. Activation of mGluR7s inhibits cocaine-induced reinstatement of drug-seeking behavior by a nucleus accumbens glutamate-mGluR2/3 mechanism in rats. *J Neurochem.* 2010; 114:1368–80. [PubMed: 20534005]
17. Li X, Li J, Peng X-Q, Spiller K, Gardner EL, Xi Z-X. Metabotropic glutamate receptor 7 modulates the rewarding effects of cocaine in rats: involvement of a ventral pallidal GABAergic mechanism. *Neuropsychopharmacology.* 2009; 34:1783–96. [PubMed: 19158667]
18. McFarland K, Lapish CC, Kalivas PW. Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *J Neurosci.* 2003; 23:3531–7. [PubMed: 12716962]
19. Sanchis-Segura C, Borchardt T, Vengeliene V, Zghoul T, Bachteler D, Gass P, Sprengel R, Spanagel R. Involvement of the AMPA receptor GluR-C subunit in alcohol-seeking behavior and relapse. *J Neurosci.* 2006; 26:1231–8. [PubMed: 16436610]
20. Schmidt HD, Pierce RC. Cocaine-induced neuroadaptations in glutamate transmission: potential therapeutic targets for craving and addiction. *Ann N Y Acad Sci.* 2010; 1187:35–75. [PubMed: 20201846]
21. Stephens DN, Brown G. Disruption of operant oral self-administration of ethanol, sucrose, and saccharin by the AMPA/kainate antagonist, NBQX, but not the AMPA antagonist, GYKI 52466. *Alcohol Clin Exp Res.* 1999; 23:1914–20. [PubMed: 10630610]
22. Szénási G, Vegh M, Szabo G, Kertesz S, Kapus G, Albert M, Greff Z, Ling I, Barkoczy J, Simig G, Spedding M, Harsing LG Jr. 2,3-Benzodiazepine-type AMPA receptor antagonists and their neuroprotective effects. *Neurochem Int.* 2008; 52:166–83. [PubMed: 17707550]
23. Vorel SR, Liu X, Hayes RJ, Spector JA, Gardner EL. Relapse to cocaine-seeking after hippocampal theta burst stimulation. *Science.* 2001; 292:1175–8. [PubMed: 11349151]
24. Wise RA. Neurobiology of addiction. *Curr Opin Neurobiol.* 1996; 6:243–51. [PubMed: 8725967]
25. Xi Z-X, Gardner EL. Hypothesis-driven medication discovery for the treatment of psychostimulant addiction. *Curr Drug Abuse Rev.* 2008; 1:303–27. [PubMed: 19430578]
26. Xi Z-X, Newman AH, Gilbert JG, Pak AC, Peng X-Q, Ashby CR Jr, Gitajn L, Gardner EL. The novel dopamine D3 receptor antagonist NGB 2904 inhibits cocaine's rewarding effects and cocaine-induced reinstatement of drug-seeking behavior in rats. *Neuropsychopharmacology.* 2006; 31:1393–405. [PubMed: 16205781]

Highlights

- GYKI 52466 is a systemically active non-competitive AMPA receptor antagonist
- GYKI 52466 (1, 3, 10 mg/kg) did not alter cocaine self-administration
- GYKI 52466 (3, 10 mg/kg) did not alter cocaine-evoked reinstatement of drug seeking
- These findings suggest GYKI 52466 has low potential for cocaine addiction treatment

Figure 1. Effects of GYKI 52466 on total number of self-administered cocaine infusions
Data are presented as total number of cocaine infusions after different doses of GYKI 52466 or vehicle (means $\pm$ SEM). Across all subjects, GYKI 52466 at 1, 3, or 10 mg/kg (i.v.) did not significantly alter cocaine-self-administration under FR2 reinforcement.

Figure 2. Effects of GYKI 52466 on cocaine-triggered reinstatement of drug-seeking behavior Lever press responses during the last day of cocaine self-administration, the last day of extinction, and the reinstatement test day are shown. During reinstatement, each dose of GYKI 52466 or vehicle was followed by a 10 mg/kg (i.p.) priming injection of cocaine to assess cocaine-induced drug-seeking behavior. Values are presented as means $\pm$ SEM.

2A: Active lever-presses. Cocaine-priming (10 mg/kg, i.p.) significantly increased active lever press responding during reinstatement testing ($*p < 0.05$, when compared to extinction levels). GYKI 52466 (3, 10 mg/kg, i.v.) pretreatment did not alter cocaine-triggered reinstatement of drug-seeking behavior as compared to vehicle control group ($p = .96$).

2B: Inactive lever-presses. GYKI 52466 and/or cocaine priming had no effect on inactive lever responses as compared to vehicle control group ($p = .86$).