1999

# Serotonin2C receptors appear to mediate genetic sensitivity to cocaine-induced convulsions

Laura O'Dell, *University of Texas at El Paso*

Psychopharmacology (1999) 146:313–319 

ORIGINAL INVESTIGATION

**L.E. O'Dell · M.J. Kreifeldt · F.R. George · M.C. Ritz**

# Serotonin$_{2C}$ receptors appear to mediate genetic sensitivity to cocaine-induced convulsions

Received: 17 February 1999 / Final version: 17 May 1999

**Abstract** *Rationale*: C57BL/6ByJ (6ByJ) and C57BL/6J (6J) mice differ in their sensitivity to cocaine-induced convulsions, with $CD_{50}$ values being 100 and 70 mg/kg, respectively. This genetic sensitivity to cocaine-induced convulsions is probably related to 5-HT$_2$ receptors, since the density of these sites and the concentration of 5-HT$_2$ antagonists required to block cocaine-induced convulsions is lower in 6J mice relative to 6ByJ mice. *Objective*: Although 5-HT$_2$ receptors appear to play a role in mediating genetic sensitivity to cocaine-induced convulsions, the role of 5-HT$_2$ receptor subtypes in this effect of cocaine has not been examined. *Methods*: The present study compared the effects of the preferential 5-HT$_{2C}$ agonists *m*-chlorophenylpiperazine (mCPP) and 6-chloro-2-(1-piperazinyl)pyrazine (MK212) on cocaine-induced convulsions in 6ByJ and 6J mice. General activity was also measured following pretreatment with mCPP and MK212. *Results*: Both mCPP and MK212 potentiated cocaine-induced convulsions and the effect of these agonists was more robust in 6ByJ mice relative to 6J mice. *Conclusion*: The findings from this study support previous research suggesting that 5-HT$_2$ receptors play a role in mediating cocaine-induced convulsions, and extend previous research by suggesting that the 5-HT$_{2C}$ receptor subtype mediates cocaine-induced convulsions and genetic sensitivity to this toxic effect of cocaine.

**Key words** mCPP · MK212 · Cocaine · Serotonin · Convulsion

## Introduction

Converging lines of evidence suggest that serotonin (5-HT) neurotransmission plays a key role in mediating cocaine-induced convulsions. Using multiple receptor site analyses, we demonstrated that convulsions produced by cocaine and related compounds are associated with binding of these compounds to the 5-HT transporter (Ritz and George 1993). Pharmacological studies support the role of 5-HT in mediating cocaine-induced convulsions, since this effect is enhanced by pretreatment with 5-HT reuptake inhibitor (SSRI) compounds such as fluoxetine (Ritz and George 1997), paroxetine, and citalopram (O'Dell et al. 1999). More specifically, the role of 5-HT in mediating cocaine-induced convulsions appears to be mediated through the actions of these compounds at 5-HT$_2$ receptors, since cocaine-induced convulsions are attenuated by the 5-HT$_2$ receptor antagonists cinanserin and ketanserin (Schechter and Meehan 1995; Ritz and George 1997). These studies demonstrate that 5-HT neurotransmission, acting primarily at 5-HT$_2$ receptors, plays an important role in mediating cocaine-induced convulsions.

Recent pharmacogenetic studies in our laboratory implicate the role of 5-HT$_2$ receptors in mediating sensitivity to cocaine-induced convulsions. In an initial pharmacogenetic screen, we found that C57BL/6J (6J) mice are nearly twice as sensitive to cocaine-induced convulsions relative to the closely related substrain C57BL/6ByJ (6ByJ). This finding is compelling in light of the extremely close genetic relationship between these strains of mice, with 6ByJ mice having been derived from a population of previously highly inbred 6J mice. We also recently found that 6ByJ mice have a higher density of 5-HT$_2$ receptors across several brain regions and that these mice require a higher concentration of cinanserin to attenuate cocaine-induced convulsions relative to 6J mice (O'Dell et al. 1998). This finding that mice with fewer 5-HT$_2$ receptors are more sensitive to cocaine-induced convulsions is interesting in light of research indicating that mutant mice lacking 5-HT$_{2C}$ receptors display heightened susceptibility to sound-induced audiogenic seizures (Brennan et al. 1997).

Our pharmacology studies using cinanserin and ketanserin support the role of 5-HT$_2$ receptors in mediating cocaine-induced convulsions. However, it remains

L.E. O'Dell · M.J. Kreifeldt · F.R. George · M.C. Ritz
Amethyst Technologies, Inc., 1435 North Hayden Road, Scottsdale, AZ 85257-3773, USA
e-mail: lauraodell@aol.com, Fax: +1-602-970-6355

unclear which 5-$HT_2$ receptor subtype(s) mediate(s) this effect. Peroutka (1994) reported that compounds such as cinanserin exhibit approximately 30-fold selectivity for 5-$HT_{2A}$ sites relative to 5-$HT_{2C}$ sites. Although this suggests that the effects of cinanserin on convulsions is due to blockade of 5-$HT_{2A}$ sites, more research is needed to examine the role of other 5-$HT_2$ receptor subtypes in mediating sensitivity to cocaine-induced convulsions.

In order to examine the role of 5-$HT_{2C}$ receptors in mediating sensitivity to the convulsant effects of cocaine, this study compared the effects of the preferential 5-$HT_{2C}$ agonists *m*-chlorophenylpiperazine (mCPP) and 6-chloro-2-(1-piperazinyl)pyrazine (MK212) on cocaine-induced convulsions across 6ByJ and 6J mice. Indeed, mCPP is 10-fold more selective and MK212 is 25- to 50-fold more selective for 5-$HT_{2C}$ receptors relative to 5-$HT_{2A}$ sites (see Kennett 1993, 1997). This study extends previous work in our laboratory by examining the effects of agonists with preferential selectivity for 5-$HT_{2C}$ sites on cocaine-induced convulsions. We also examined the effects of mCPP and MK212 on behavioral activity, to determine whether the effects of serotonergic compounds on convulsions might be related to motor effects produced by these drugs.

On an a priori basis, two of several possible outcomes would provide the most important information. First, if these agonists attenuate cocaine-induced convulsions, then 5-$HT_{2C}$ receptors likely play an inhibitory role in mediating this effect of cocaine, consistent with results indicating that C57 mice have fewer 5-$HT_2$ receptors and are more sensitive to cocaine-induced convulsions relative to CBy mice. Accordingly, 5-$HT_{2C}$ agonists should attenuate this effect of cocaine more potently in mice displaying fewer 5-$HT_2$ sites. Second, if mCPP and MK212 potentiate cocaine-induced convulsions, then 5-$HT_{2C}$ sites probably play an excitatory role in mediating this effect of cocaine. This is consistent with research demonstrating that 5-$HT_2$ antagonists attenuate cocaine-induced convulsions (Schechter and Meehan 1995; Ritz and George 1997) and compounds which increase 5-HT neurotransmission facilitate this effect of cocaine (Ritz and George 1997; O'Dell et al. 1999). In this case, 5-$HT_{2C}$ agonists should produce a greater facilitation of convulsions in mice displaying more 5-$HT_2$ sites. While this outcome might seem counterintuitive to the finding that mice with more of these sites are less sensitive to cocaine-induced convulsions, one possible explanation would be that higher 5-$HT_2$ densities in 6ByJ mice are due to a compensatory upregulation of these receptors in response to lower levels of synthesized 5-HT. In this case, 6ByJ mice would require higher doses of cocaine to produce convulsions relative to 6J mice, as we have shown, and 6ByJ mice would be more sensitive to 5-$HT_2$ agonists, such as mCPP and MK212.

## Materials and methods

### Animals

Experimentally naive male 6J and 6ByJ mice (60–100 days old) were obtained from the Jackson Laboratories (Bar Harbor, Maine, USA). Animals were housed in groups of same-sex littermates in a colony room (26°C; 0700–1900 hours lights on) which was maintained in accordance with the Guide for Care and Use of Laboratory Animals provided by the National Institute of Health.

### Behavioral observations

The effects of mCPP and MK212 on cocaine-induced convulsions were compared in 6J and 6ByJ mice. Animals received an injection of saline, mCPP (10, 30 mg/kg), or MK212 (10, 30 mg/kg). Each treatment group included 4–12 mice. All drug doses are expressed as mg/kg base and were administered intraperitoneally in a volume of 10 ml/kg of 0.9% saline. Mice were then placed into 30×30 $cm^2$ Plexiglas chambers with the floor of the chambers divided into four equal quadrants. During the initial 15-min observation period, some of the mice from each treatment group ($n$=4 at least per group) were monitored for behavioral activity, which was measured as the number of crosses between each individual quadrant (i.e., quadrant crosses).

Animals then received an injection of (–)-cocaine HCl (32, 42, 56, 75, 100, or 133 mg/kg) and were monitored by a "blind" observer for an additional 15 min for the occurrence and latency of any of the following behavioral indices of convulsant activity typically produced by cocaine: wild running, clonus, tonus, and clonic-tonic (Ritchie and Greene 1985). Animals were observed for 15 min, since initial studies indicate that the percentage of convulsions occurring within 15 or 60 min post-injection does not differ, and this effect typically occurs within 2–4 min post-injection.

### Statistics

$CD_{50}$ (mg/kg) values for convulsions were determined by linear regression analyses of the resultant dose-response curves. The effects of mCPP and MK212 on cocaine-induced convulsions were analyzed using logistic regression. The interaction between cocaine and mCPP or MK212 was used to assess parallelism as an indicator of competitive or noncompetitive effects. The effects of mCPP and MK212 on quadrant crosses were analyzed using overall ANOVAs with Fisher's PLSD post-hoc analyses ($P$<0.05).

## Results

### Strain differences in cocaine-induced convulsions

Figure 1 illustrates the percentage of convulsions produced by cocaine in 6J (circles) and 6ByJ (squares) mice. Cocaine administration produced convulsions in both strains of mice; however, 6J and 6ByJ mice differed significantly in their sensitivity to this effect of cocaine, with $CD_{50}$ values being 70 and 100 mg/kg, respectively ($P$<0.005). The $CD_{50}$ for 6J mice in the present study is modestly but not significantly different from the originally reported value of 60 mg/kg, which was determined in animals that did not receive saline pretreatment (O'Dell et al. 1998). The $CD_{50}$ in 6ByJ mice did not differ from previous reports using non-saline-pretreated animals.

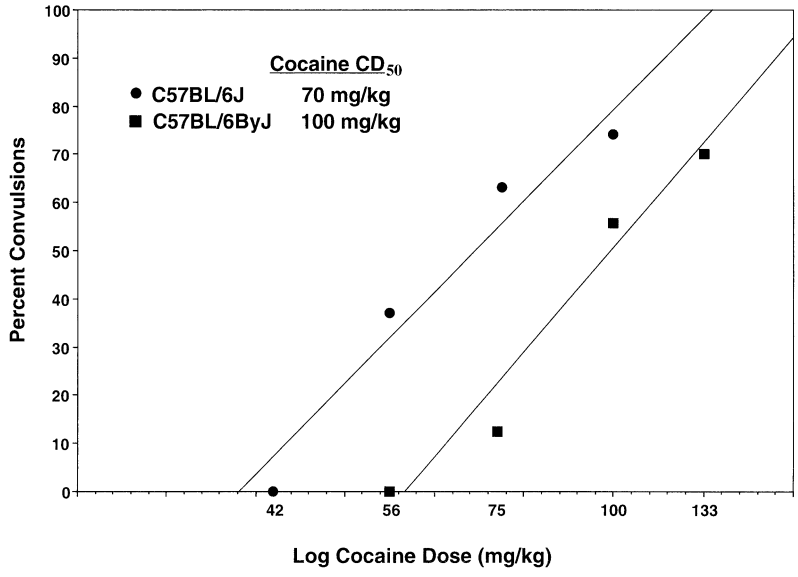


**Fig. 1** Percentage of convulsions produced by cocaine in 6ByJ (*squares*) and 6J (*circles*) mice. Cocaine administration produced convulsions in both strains of mice, however, 6J and 6ByJ mice differ significantly in their sensitivity to this effect, with $CD_{50}$ values being 70 and 100 mg/kg, respectively

mCPP effects on cocaine-induced convulsions

Figure 2 illustrates the effects of mCPP on cocaine-induced convulsions in 6ByJ mice. Pretreatment with mCPP produced an overall potentiation of cocaine-induced convulsions ($P<0.0001$) that was significantly increased by the 10 and 30 mg/kg dose of mCPP ($P<0.05$ and $P<0.003$, respectively). The $CD_{50}$ decreased from 100 mg/kg in control mice to 77.6 mg/kg in mice receiving 10 mg/kg mCPP and 50.1 mg/kg in mice receiving 30 mg/kg mCPP. Both doses of this agonist shifted the cocaine dose-response curve to the left in a parallel fashion, suggesting a competitive agonist action of mCPP.

Figure 3 illustrates the effects of mCPP on cocaine-induced convulsions in 6J mice. Pretreatment with mCPP produced an overall potentiation of cocaine-induced convulsions ($P<0.01$) that was significantly increased by the 30 mg/kg dose of mCPP ($P<0.01$). The $CD_{50}$ decreased from 70 mg/kg in control mice to 48.9 mg/kg in mice receiving 30 mg/kg mCPP.

mCPP significantly shifted the cocaine dose-response curve to the left in a parallel fashion in both strains, suggesting that the effects of mCPP on cocaine-induced convulsions are probably mediated by the same neural mechanism. Although mCPP facilitated cocaine-induced convulsions in both strains of mice, the effect of mCPP was more robust in 6ByJ relative to 6J mice. For example, 10 mg/kg mCPP decreased the cocaine $CD_{50}$ nearly twice as much in 6ByJ (22% decrease) relative to 6J (12% decrease) mice. Similarly, 30 mg/kg mCPP also decreased the cocaine $CD_{50}$ much more robustly in 6ByJ relative to 6J mice (50% versus 30% decrease, respectively).

MK212 effects on cocaine-induced convulsions

Figure 4 illustrates the effects of MK212 on cocaine-induced convulsions in 6ByJ mice. Pretreatment with MK212 produced an overall potentiation of cocaine-induced convulsions ($P<0.001$) that was due primarily to a significant increase at the 30 mg/kg dose of MK212 ($P<0.001$). The 30 mg/kg dose of MK212 shifted the $CD_{50}$ from 100 mg/kg to 60.2 mg/kg. MK212 appeared to shift the cocaine dose-response curve to the left in a parallel fashion, suggesting a competitive agonist action of MK212.

Figure 5 illustrates the effects of MK212 on cocaine-induced convulsions in 6J mice. While MK212 did produce a moderate shift to the left in the cocaine $CD_{50}$, this compound did not produce any significant changes in cocaine-induced convulsions in 6J mice. With MK212 pretreatment, the $CD_{50}$ was decreased from 70 mg/kg in control mice to 64.5 mg/kg in mice receiving 10 mg/kg MK212 and 60.25 mg/kg in mice receiving 30 mg/kg MK212.

Thus, MK212 significantly facilitated cocaine-induced convulsions in 6ByJ, but produced only a trend towards agonist activity in 6J mice. Similar to mCPP, MK212 produced a more robust shift in 6ByJ mice relative to 6J mice. The 30 mg/kg dose of MK212 shifted the cocaine $CD_{50}$ nearly three times more in 6ByJ mice (40% decrease) relative to 6J mice (14% decrease).

mCPP and MK212 effects on behavioral activity

Figure 6 illustrates the effects of mCPP and MK212 on behavioral activity in 6ByJ and 6J mice. Both mCPP and MK212 produced a decrease in behavioral activity in both strains of mice relative to their respective saline controls. mCPP produced a decrease in behavioral activity [$F(5,51)=45.12$, $P<0.0001$] across both strains of mice that was significant at the 10 and 30 mg/kg dose of mCPP relative to their respective saline controls ($P<0.0001$). MK212 also produced a decrease in behavioral activity [$F(5,29)=58.4$, $P<0.0001$] across both

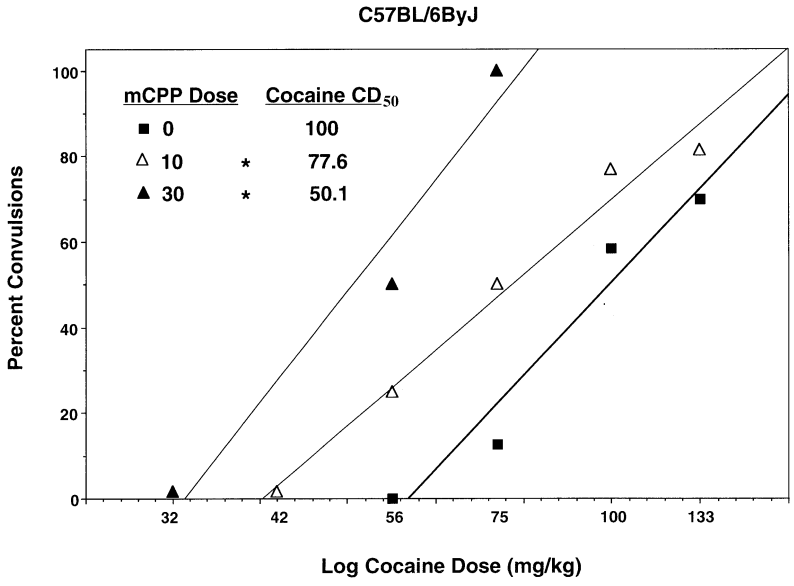


**Fig. 2** mCPP effects on cocaine-induced convulsions in 6ByJ mice. Pretreatment with mCPP produced an overall potentiation of cocaine-induced convulsions that was significantly increased by the 30 mg/kg dose of mCPP. **Asterisks* denote a significant shift in the cocaine dose-response curve relative to mice receiving saline pretreatment

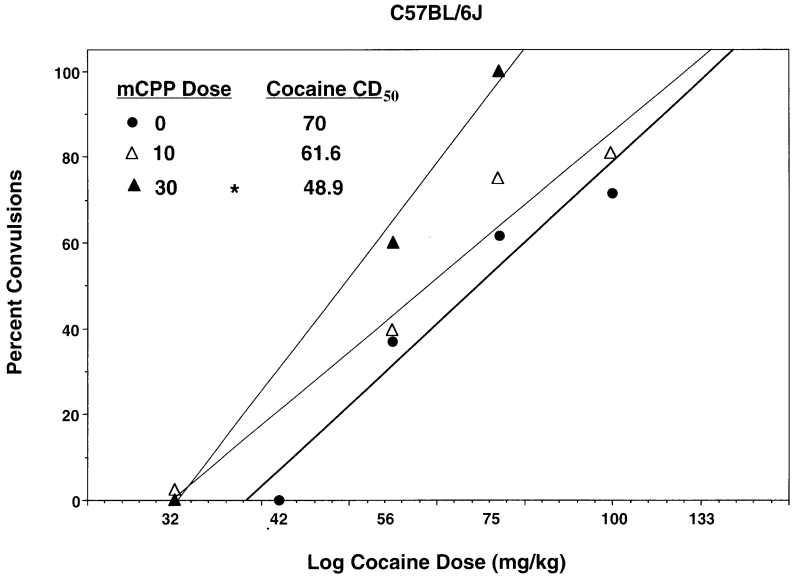


**Fig. 3** mCPP effects on cocaine-induced convulsions in 6J mice. Pretreatment with mCPP produced an overall potentiation of cocaine-induced convulsions that was significantly increased by the 10 and 30 mg/kg dose of mCPP. **Asterisks* denote a significant shift in the cocaine dose-response curve relative to mice receiving saline pretreatment

strains of mice that was significant at the 10 and 30 mg/kg dose of MK212 relative to their respective saline controls ($P<0.001$). There were no strain differences in baseline activity or in the attenuation of activity produced by mCPP or MK212.

## Discussion

This study supports the hypothesis that 5-HT neurotransmission, acting primarily via 5-$HT_2$ receptors, plays an important role in mediating cocaine-induced convulsions. This hypothesis was originally based on findings from our laboratory demonstrating that there is a significant correlation between the ability of cocaine-like compounds to produce convulsions with the affinity of these compounds at 5-HT uptake sites (Ritz and George 1993). Subsequent research implicated 5-$HT_2$ sites in mediating cocaine-induced convulsions, since this effect was attenuated by the 5-$HT_2$ receptor antagonists, cinanserin and ketanserin (Schechter and Meehan 1995; Ritz and George 1997). This study further supports the role of 5-$HT_2$ receptors in mediating this toxic effect of cocaine. This is based on the finding that the 5-$HT_2$ agonists used in this study produced parallel leftward shifts in the cocaine dose-response curve for convulsions. The competitive agonism of these compounds suggests that these compounds altered this toxic effect of cocaine via the same direct receptor-mediated neural mechanism. Since mCPP has little relative affinity for non-5-HT systems, with the exception of $\alpha_2$ adrenergic sites (Hamick and Peroutka 1989), and we have demonstrated that the $\alpha_2$ antagonist yohimbine does not alter cocaine-induced convulsions (Ritz and George 1997), it is unlikely that

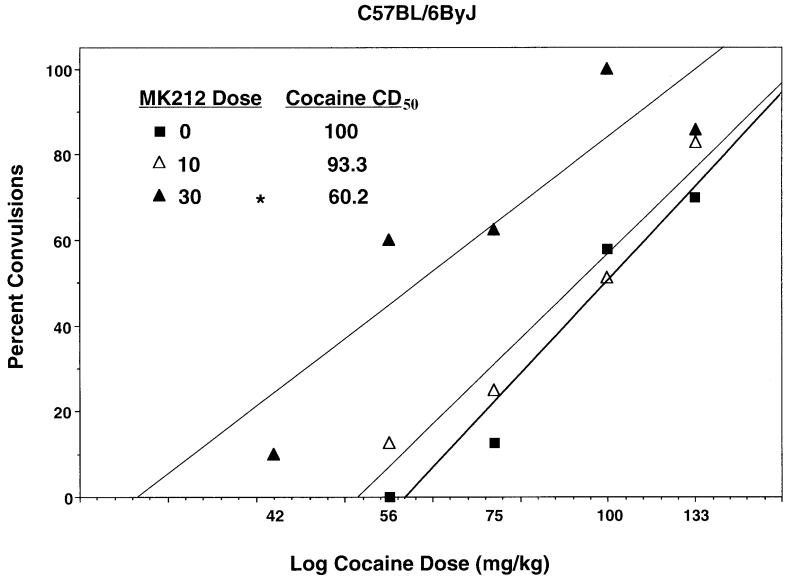


**Fig. 4** MK212 effects on cocaine-induced convulsions in 6ByJ mice. Pretreatment with MK212 produced an overall potentiation of cocaine-induced convulsions that was significantly increased by the 30 mg/kg dose of MK212. **Asterisks* denote a significant shift in the cocaine dose-response curve relative to mice receiving saline pretreatment

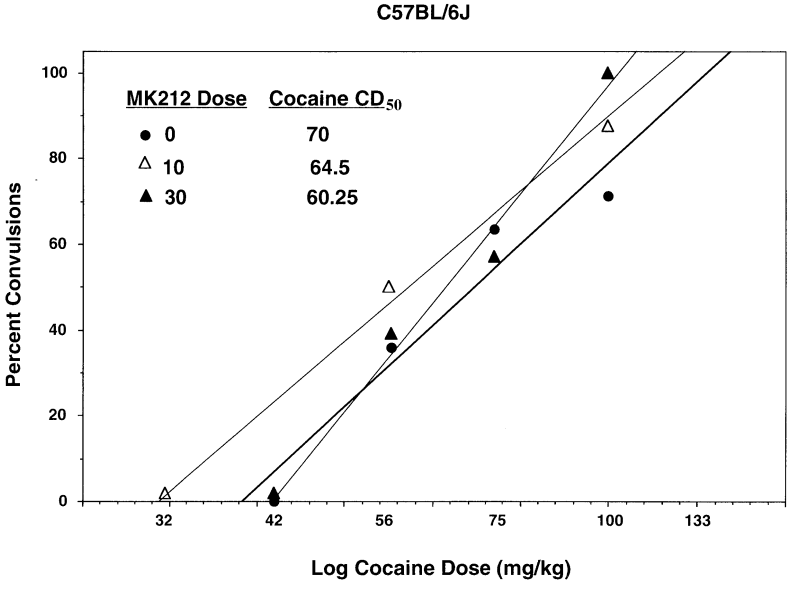


**Fig. 5** MK212 effects on cocaine-induced convulsions in 6J mice. Pretreatment with MK212 did not significantly alter the incidence of cocaine-induced convulsions

these compounds altered this effect of cocaine via another neurotransmitter system.

Previous research in our laboratory has demonstrated that 5-$HT_2$ receptors mediate genetic sensitivity to cocaine-induced convulsions. We found that 6J mice are nearly twice as sensitive to cocaine-induced convulsions relative to 6ByJ mice. Interestingly, 6J mice have a lower density of 5-$HT_2$ receptors and require lower doses of the 5-$HT_2$ antagonist cinanserin to block cocaine-induced convulsions relative to 6ByJ mice (O'Dell et al. 1998). Despite the fact that both cinanserin and ketanserin exhibit a high affinity for 5-$HT_2$ sites (1–4 nM), these compounds are generally considered to be non-selective 5-$HT_2$ antagonists (see Martin and Humphrey 1993 ; Peroutka 1994). Therefore, although our findings suggested that 5-$HT_2$ sites play a role in mediating genetic sensitivity to cocaine-induced convulsions, it was unclear which 5-$HT_2$ receptor subtype mediated this effect.

The present study extends previous research by suggesting that 5-$HT_{2C}$ receptors mediate genetic sensitivity to cocaine-induced convulsions. This is based on the finding that agonists which preferentially bind to 5-$HT_{2C}$ receptors produce a more robust facilitation of convulsions in 6ByJ mice relative to 6J mice. Indeed, mCPP is 10-fold and MK212 is 25- to 50-fold more selective for 5-$HT_{2C}$ relative to 5-$HT_{2A}$ sites (see Kennett 1993, 1997). Moreover, pharmacological studies suggest that the behavioral effects of these compounds are due to activation of 5-$HT_{2C}$ receptors. For example, Kennett and Curzon (1991) demonstrated that the $ID_{50}$ values of a series of antagonists to block mCPP-induced hypothermia were directly proportional to the affinity of these compounds for 5-$HT_{2C}$ receptors. In addition, mCPP-induced

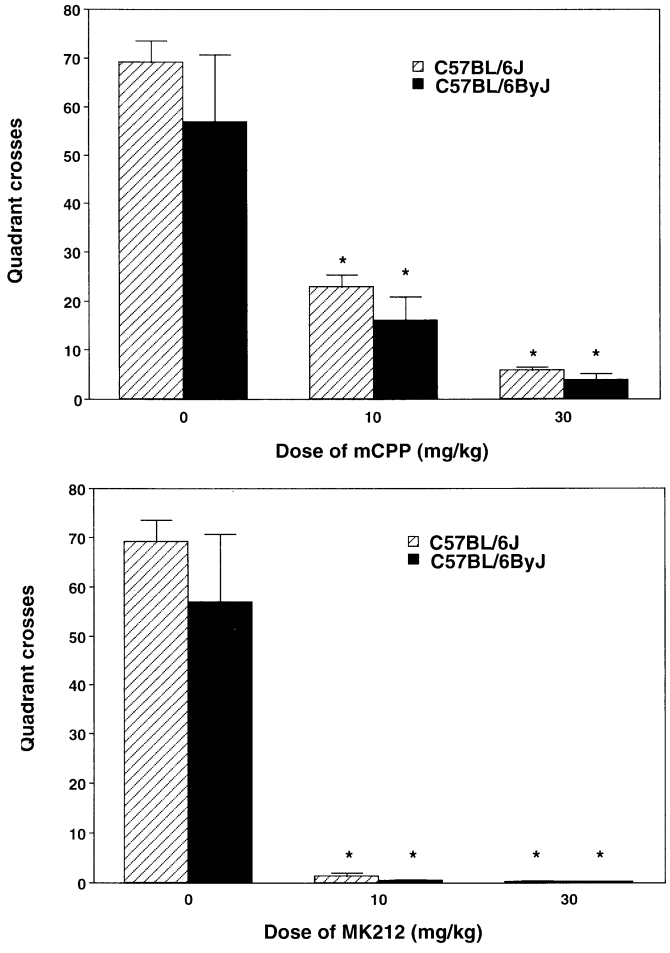


**Fig. 6** mCPP (*top panel*) and MK212 (*bottom panel*) effects on behavioral activity (i.e., quadrant crosses) in 6ByJ (*solid bars*) and 6J (*hatched bars*) mice. The number of quadrant crosses did not differ between 6ByJ and 6J mice. Both mCPP and MK212 produced a potent decrease in quadrant crosses that did not differ across these strains of mice. **Asterisks* denote a significant difference relative to their respective saline controls

hypolocomotion is attenuated by non-selective 5-$HT_{2A/2C}$ antagonists, but not by more selective 5-$HT_{2A}$ antagonists, such as ketanserin (Kennett and Curzon 1988; Klodzinska et al. 1989; Lucki et al. 1989). Other lines of research have also suggested that the discriminative stimulus properties of mCPP and MK212 are mediated by 5-$HT_{2C}$ receptors (Cunningham et al. 1986; Fiorella 1995; Gommans et al. 1998). Callahan and Cunningham (1995) have also utilized mCPP and MK212 to demonstrate the role of 5-$HT_{2C}$ receptors in mediating the discriminative stimulus effects of cocaine. These studies illustrate that mCPP and MK212 are useful pharmacological tools for examining behavioral effects produced by 5-$HT_{2C}$ receptor activation.

Additional biochemical findings support the hypothesis that effects of mCPP and MK212 on cocaine-induced convulsions may be due to selective activation of 5-$HT_{2C}$ versus 5-$HT_{2A}$ receptors. First, it has been demonstrated that mCPP and MK212 produce stimulation of phosphoinositide (PI) hydrolysis turnover in the choroid plexus, an effect that is attributed to stimulation of 5-$HT_{2C}$ receptors (Conn and Sanders-Bush 1987). However, the latter study demonstrated that MK212, but not mCPP, produces stimulation of PI hydrolysis turnover in the frontal cortex, an effect that is attributed primarily to stimulation of 5-$HT_{2A}$ receptors. Based on this study, it has been suggested that mCPP is an antagonist, or possibly a partial agonist, at 5-$HT_{2A}$ sites (see Kennett 1997). In the present study, if the effects of mCPP were due in any significant way to activation of 5-$HT_{2A}$ sites, then one might expect that this compound might have either no effect or a reduced effectiveness in potentiating cocaine-induced convulsions. However, in both strains of mice mCPP facilitated cocaine-induced convulsions beyond control values and produced robust parallel leftward shifts in the cocaine $CD_{50}$ values. Second, we observed that these compounds produced an increase in head twitches, a behavior that is believed to be due to activation of 5-$HT_{2A}$ sites (see Schreiber et al. 1995; Durson and Handley 1996). However, the emergence of this behavior did not appear to differ across these strains of mice (data not shown). Based on these studies, we suggest that the effects of mCPP and MK212 on cocaine-induced convulsions were due to activation of 5-$HT_{2C}$ receptors and that these sites mediate genetic sensitivity to this toxic effect of cocaine.

The effects of serotonergic compounds on cocaine-induced convulsions could be related to their motor effects. For example, in addition to decreasing cocaine-related convulsions, cinanserin and ketanserin attenuate behavioral activity (Ritz and George 1997). However, the present study demonstrated that both mCPP and MK212 attenuated locomotor activity while enhancing cocaine-induced convulsions. Furthermore, previous research has demonstrated that the hypolocomotion produced by mCPP is related to anxiogenic effects (Kennett et al. 1989). Therefore, the effects of serotonergic compounds on cocaine-induced convulsions are probably not related to motoric effects. It is also important to note that the effects of mCPP and MK212 on locomotor activity did not differ across these strains of mice, further distinguishing the locomotor effects of 5-HT compounds from their ability to regulate the expression of cocaine-induced convulsions.

The present findings further support an important role for 5-$HT_2$, and possibly 5-$HT_{2C}$ receptors, in mediating genetic sensitivity to cocaine-induced convulsions. It was suggested that 5-$HT_{2C}$ sites may play an inhibitory role in mediating cocaine-induced convulsions, since 6ByJ mice have a higher density of 5-$HT_2$ sites and require a higher dose of cinanserin to block cocaine-induced convulsions even though they are less sensitive to the convulsant effects of cocaine relative to 6J mice (O'Dell et al. 1998). However, the present study suggests that 5-$HT_{2C}$ sites play a facilitatory role in mediating cocaine-induced convulsions, since compounds that activate 5-$HT_{2C}$ sites facilitate cocaine-induced convulsions and this effect is more robust in mice displaying a higher density of 5-$HT_2$ receptors. As a result, the relationship between sensitivity to cocaine-induced convulsions, den-

sity of 5-$HT_2$ sites, and pharmacological effects of 5-$HT_2$ compounds might seem counterintuitive. One possible explanation is that the higher density of 5-$HT_2$ sites in 6ByJ mice results from a compensatory upregulation of these receptors in response to lower levels of synthesized 5-HT. In this case, it would be expected that 6ByJ mice would require higher doses of cocaine to produce convulsions relative to 6J mice, consistent with previous and present findings. Furthermore, consistent with the present findings, 6ByJ mice would be more sensitive to the effects of 5-$HT_2$ agonists, since these mice have a higher density of these receptors relative to 6J mice. Ongoing research is examining aspects of 5-HT synthesis that may play a role in mediating sensitivity to the toxic effects of cocaine.

**Acknowledgements** This research was supported by the National Institute on Drug Abuse at the National Institutes of Health via grant DA 07767 to M. C. R. and DA07767-04S1 to L. E. O. and by Amethyst Technologies, Inc. The opinions expressed herein are solely those of the authors and do not necessarily represent official positions of the National Institutes of Health or Amethyst Technologies, Inc.

## References

Brennan TJ, Seeley WW, Kilgard M, Schreiner CE, Tecott LH (1997) Sound-induced seizures in serotonin 5-$HT_{2C}$ receptor mutant mice. Nat Genet 16-387–390

Callahan PM, Cunningham KA (1995) Modulation of the discriminative stimulus properties of cocaine by 5-$HT_{1B}$ and 5-$HT_{2C}$ receptors. J Pharmacol Exp Ther 274:1414–1424

Conn, Sanders-Bush (1987) Relative efficacies of piperazines at the phosphoinositide hydrolysis-linked serotonergic (5-$HT_2$ and 5-$HT_{1C}$) receptors. J Pharmacol Exp Ther 242:552–557

Cunningham KA, Callahan PM, Appel JB (1986) Discriminative stimulus properties of the serotonin agonist MK 212. Psychopharmacology 90:193–197

Durson SM, Handley SL (1996) Similarities in the pharmacology of spontaneous and DOI-induced head-shakes suggest 5-$HT_{2A}$ receptors are active under physiological conditions. Psychopharmacology 128:198–205

Fiorella D, Rabin RA, Winter JC (1995) The role of the 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors in the stimulus effects of *m*-chlorophenylpiperazine. Psychopharmacology 119:222–230

Gommans J, Hijzen TH, Maes RAA, Olivier B (1998) Discriminative stimulus properties of mCPP: evidence for a 5-$HT_{2C}$ receptor mode of action. Psychopharmacology 137:292-302

Hamick A, Peroutka SJ (1989) 1-(*m*-Chloro-phenyl)piperazine interactions with neurotransmitters in the human brain. Biol Psychol 25:569–575

Kennett GA (1993) 5-$HT_{1C}$ receptors and their therapeutic relevance. Curr Opin Invest Drugs 2:317–362

Kennett GA (1997) Serotonin receptors and their function. Smith-Kline Beecham Pharmaceuticals, published by Tocris Cooksen Inc.

Kennett GA, Curzon G (1988) Evidence that mCPP may have behavioral effects mediated by central 5-$HT_{1C}$ receptors. Br J Pharmacol 94:137–147

Kennett GA, Curzon G (1991) Potencies of antagonists indicate that 5-$HT_{1C}$ receptors mediate 1-3(chlorophenyl)piperazine induced hypophagia. Br J Pharmacol 103:2016–2020

Kennett GA, Whitton P, Curzon G (1989) Anxiogenic-like effects of mCPP and TFMPP in animal models are opposed by 5-$HT_{1C}$ receptor antagonists. Eur J Pharmacol 164:445–454

Klodzinska A, Jaros T, Chojnacka-Wojik E, Maj J (1989) Exploratory hypoactivity induced by *m*-trifluoromethylphenylpiperazine (TFMPP) and *m*-chlorophenylpiperazine (m-CPP). J Neural Transm 1:207–218

Martin GR, Humphrey PPA (1993) Receptors for 5-HT: current perspectives on classification and nomenclature. Neuropharmacology 33:261–273

Lucki I, Ward HR, Frazer A (1989) Effect of 1-(*m*-chlorophenyl)piperazine and 1-(*m*-trifluoromethylphenyl) piperazine on locomotor activity. J Pharmacol Exp Ther 249:155-164

O'Dell LE, Kreifeldt MJ, George FR, Ritz MC (1998) Cocaine-induced convulsions: 5-$HT_2$ receptor densities contribute to genetic differences. Soc Neurosci Abstr 42:2171

O'Dell LE, George FR, Ritz MC (1999) Antidepressant compounds appear to enhance cocaine-induced convulsions. Clin Exp Psychopharmacol (in press)

Peroutka SJ (1994) Molecular biology of serotonin (5-HT) receptors. Synapse 18:241–260

Ritchie JM, Greene NM (1985) Local anesthetics. In: Gilman AG, Goodman LS, Gilman A (eds) The pharmacological basis of therapeutics, 6th edn. Macmillan, New York, pp 300–320

Ritz MC, George FR (1993) Cocaine-induced seizures and lethality appear to be associated with distinct central nervous system binding sites. J Pharmacol Exp Ther 264:1333–1343

Ritz MC, George FR (1997) Cocaine-induced convulsions: pharmacological antagonism at serotonergic, muscarinic, and sigma receptors. Psychopharmacology 129:299–310

Schechter MD, Meehan SM (1995) Serotonergic mediation of cocaine seizures in mice. Pharmacol Biochem Behav 51:313–316

Schreiber R Brocco M, Audinot V, Gobert A, Veiga S, Millan MJ (1995) (1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane)-induced head-twitches in the rat are mediated by 5-hydroxytryptamine (5-HT)$_{2A}$ receptors: modulation by novel 5-$HT_{2A/2C}$ antagonists, $D_1$ antagonists and 5-$HT_{1A}$ antagonists. J Pharmacol Exp Ther 273:101–112