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Effects of AMPA/kainate glutamate receptor antagonists on cocaine-induced convulsions and lethality in mice

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Abstract

Prior studies demonstrate that NMDA receptor antagonists attenuate cocaine-induced convulsions and lethality. Since glutamate is the primary neurotransmitter for NMDA receptors, pharmacological interventions to lower glutamatergic activity through non-NMDA ionotropic receptor-mediated mechanisms were evaluated for their ability to prevent the convulsive and lethal effects of cocaine. Pre-treatment of male, Swiss Webster mice with the α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)/kainate receptor antagonists 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide (NBQX; 10–80 mg/kg, i.p.) or 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine hydrochloride (GYKI 52466; 10–20 mg/kg, i.p.) failed to significantly attenuate cocaine-induced convulsions or lethality. Although ineffective when administered alone, NBQX enhanced the protective effects of 5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione (ACEA-1021), an NMDA/glycine site antagonist, when administered in combination. The mixed NMDA/non-NMDA receptor competitive antagonist 5-chloro-7-trifluoromethyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (ACEA-1011) also protected against the convulsive effects of cocaine. The data suggest that AMPA/kainate receptors indirectly influence the pathophysiological changes that occur after a cocaine overdose through modulation of NMDA receptors.

Keywords: Cocaine; Convulsion; Toxicity; AMPA receptor; Kainate receptor; NMDA receptor

1. Introduction

The glutamatergic system has recently been implicated in cocaine addiction (Mash et al., 1995, McGinty, 1995; Itzhak and Ali, 1998). Glutamate acts through two different ionotropic receptors, namely NMDA and non-NMDA receptors. The non-NMDA receptors are further divided into two subtypes, α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) and kainate. Previous studies have shown that antagonism of NMDA receptors attenuates the psychostimulant and reinforcing properties of cocaine (Pulvirenti et al., 1992, 1994, 1997). In addition, both AMPA and kainate receptor antagonists have been reported to reduce cocaine-induced locomotor sensitization (Karler et al., 1994; Li et al., 1997; Jackson et al., 1998), self-administration (Jackson et al., 1998), and conditioned place preference (Cervo and Samanin, 1995).

The glutamatergic system also appears to have a role in the toxic effects of cocaine. Previous studies have shown that NMDA receptor antagonists attenuate cocaine-induced convulsions and lethality (Rockhold et al., 1991; Witkin and Tortella, 1991; Itzhak and Stein, 1992; Matsumoto et al., 1997, 1998). However, the involvement of non-NMDA receptors in the convulsive and lethal effects of cocaine has yet to be evaluated. Therefore, antagonists that target non-NMDA ionotropic glutamate (AMPA/kainate) receptors were evaluated for their ability to attenuate cocaine-induced convulsions and lethality in mice.

In the present study, 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide (NBQX) or 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*- 2, 3- benzo-diazepine hydrochloride (GYKI 52466) was used to antagonize AMPA/kainate receptors. NBQX and GYKI 52466 are capable of acting through both AMPA and kainate receptors (Bleakman et al., 1996; Liu et al., 1997;

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Ohno et al., 1998; Stefani et al., 1998), and they have high affinity and selectivity for these ionotropic non-NMDA receptors, as compared to other glutamatergic receptors (Sheardown et al., 1990; Rogawski, 1993; Zormuski et al., 1993).

In addition to evaluating the anti-cocaine effects of the non-NMDA receptor antagonists on their own, the effectiveness of NBQX was tested in combination with ACEA-1021, an NMDA/glycine site antagonist. This combination was evaluated because previous studies have reported the ability of NBQX to potentiate the anticonvulsant and neuroprotective actions of NMDA receptor antagonists (Zarnowski et al., 1993; Lippert et al., 1994). Efforts were made to determine whether NBQX could improve the effectiveness of ACEA-1021 because in previous studies, ACEA-1021 was very effective against cocaine-induced convulsions, but its clinical potential was limited by a narrow therapeutic margin (Matsumoto et al., 1997). To further evaluate the effectiveness of antagonizing both NMDA and non-NMDA receptors, ACEA-1011, which antagonizes both NMDA and AMPA/kainate receptors (Woodward et al., 1995a), was tested. A portion of this work was published as an abstract (Pouw et al., 1998).

2. Materials and methods

2.1. Drugs

1,2,3,4-Tetrahydro-6-nitro-2,3-dioxo-benzo[*f*]quinoxaline-7-sulfonamide (NBQX) and 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5*H*-2,3-benzodiazepine hydrochloride (GYKI 52466 hydrochloride) were purchased from Research Biochemicals International (Natick, MA) or Tocris Cookson (St. Louis, MO). 5-Chloro-7-trifluoromethyl-1,2,3,4-tetrahydroquinoxaline-2,3-dione (ACEA-1011) and 5-nitro-6,7-dichloro-1,4-dihydro-2,3-quinoxalinedione (ACEA-1021) were obtained from CoCensys (Irvine, CA). Cocaine hydrochloride was purchased from Sigma (St. Louis, MO). Drug doses were calculated from the salt and dissolved in 50% dimethylsulfoxide (DMSO) because they are insoluble in water. The drugs were administered in a 0.1ml/10g solution.

2.2. Animals

Male, Swiss Webster mice (22–32 g; Harlan, Indianapolis, IN; Charles River, Portage, MI) were housed in groups of 4–6 on a 12 h:12 h light/dark cycle and ad libitum food and water. All experimental procedures were performed as approved by the Institutional Animal Care and Use Committee at the University of Oklahoma Health Sciences Center.

2.3. Convulsion studies

Mice were injected (i.p.) with one of the following treatments: NBQX (10, 20, 40, 80 mg/kg, $n = 38$), GYKI 52466 hydrochloride (10, 20 mg/kg, $n = 14$), saline ($n = 6$), or 50% DMSO ($n = 9$). A 15-min pre-treatment period was used for all of the antagonists except NBQX, for which a 3–5-min pre-treatment period was used; previous studies report that NBQX sometimes has short-lived effects (Taylor and Vartanian, 1992), although actions of longer duration have also been observed (Turski et al., 1992). After the appropriate pre-treatment period, the mice were challenged with a convulsive dose of cocaine (60 mg/kg, i.p.). This dose of cocaine has been shown in our hands to reliably produce convulsions in all mice tested (Matsumoto et al., 1997, 1998; McCracken et al., 1999). Following administration of cocaine, the mice were placed in individual testing boxes and watched continuously for the next 30 min for the onset of convulsions. Convulsions were operationally defined as clonic limb movements or tonic extension of the limbs, combined with the loss of righting reflexes for at least 5 s.

2.4. Lethality studies

Mice were injected (i.p.) with one of the following treatments: NBQX (20, 40, 80 mg/kg, $n = 18$), GYKI 52466 (10, 20 mg/kg, $n = 11$), saline ($n = 6$), or 50% DMSO ($n = 9$). Similar to the convulsion studies, a 15-min pre-treatment period was used for all of the antagonists except NBQX, for which a 3–5-min pre-treatment period was used. After the appropriate pre-treatment period, the mice were challenged with a lethal dose of cocaine (125 mg/kg, i.p.). This dose of cocaine, has been shown in our hands to reliably produce death in 83–100% of mice tested (Matsumoto et al., 1997, 1998; McCracken et al., 1999). Following administration of cocaine, the mice were placed in individual testing boxes and watched continuously for the next 30 min for death.

2.5. Combination treatments

Various doses of ACEA-1021 and NBQX were combined to evaluate their actions on the convulsive effects of cocaine. Mice ($n = 149$) were injected with a dose of the NMDA/glycine site antagonist ACEA-1021 (0–60 mg/kg, i.p.). Following 10–12 min, the ACEA-1021 treated animals then received a dose of NBQX (0–40 mg/kg, i.p.). For these combination pre-treatments, ACEA-1021 and NBQX were administered in half their normal volume, so that the total pre-treatment volume of drug matched earlier studies. After a subsequent 3–5 min (yielding a total of 15 min pre-treatment time for ACEA-1021), the mice received a dose of cocaine that normally produced convulsions in all animals (60 mg/kg, i.p.). The animals were observed continuously for the next 30 min for the onset of convulsions.

As an additional approach to evaluate the effects of combining NMDA/glycine site and AMPA antagonist actions, the effects of ACEA-1011, a compound with mixed NMDA and non-NMDA actions (Woodward et al.,

1995a) was tested. Mice were pre-treated with a dose of ACEA-1011 (0.1, 0.5, 0.8, 1, 2.5, 5, 10, 20, 30 mg/kg, i.p.), followed 15 min later with a convulsive dose of cocaine (60 mg/kg, i.p., $n = 73$). The proportion of mice convulsing/the total number of mice tested was recorded for each dose.

2.6. Data analysis

Fisher's exact tests (InStat, San Diego, CA) were used to determine whether pre-treatments with antagonists significantly altered the proportion of mice exhibiting cocaine-induced convulsions or lethality as compared to pre-treatments with vehicle or control. $P < 0.05$ was considered statistically significant. Protective ED_{50} values for ACEA-1011 alone, or ACEA-1021 in the presence of various doses of NBQX were calculated from the linear portion of the dose curves (InStat, San Diego, CA).

3. Results

Fisher's exact tests revealed that when administered alone, NBQX and GYKI 52466 failed to significantly alter the convulsive or lethal effects of cocaine. When NBQX was combined with the NMDA/glycine site antagonist ACEA-1021, it provided additional protective effects at some dose combinations ($P < 0.05$). The protective ED_{50} of ACEA-1021 against the convulsive effects of cocaine shifted from 41 mg/kg, i.p. to 22 mg/kg, i.p. in the presence of 10 mg/kg of NBQX, and to 20 mg/kg, i.p. in the presence of 20 mg/kg of NBQX. However, the interaction between NMDA and non-NMDA receptor mechanisms appears complex because dose-dependent, parallel shifts in the dose curve for ACEA-1021 were not observed (Fig. 1) and at the higher 40 mg/kg dose, NBQX in fact worsened the severity of the cocaine-induced convulsions. The mixed NMDA/non-NMDA receptor antagonist ACEA-1011 also provided significant protection against the convulsive effects of cocaine ($P < 0.05$; Fig. 2) with a protective ED_{50} of 1 mg/kg, i.p.

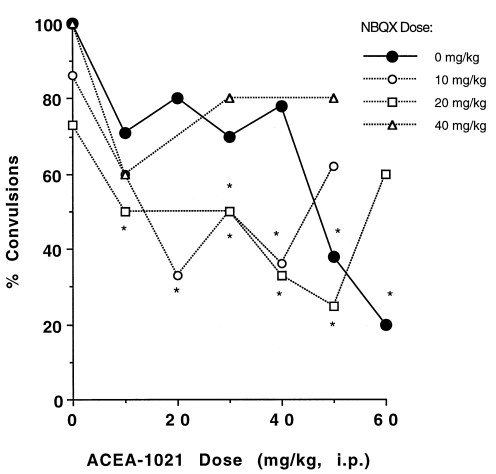

Fig. 1. Effects of the AMPA/kainate antagonist NBQX on the convulsive effects of cocaine when combined with the NMDA/glycine site antagonist ACEA-1021. Mice were pre-treated with ACEA-1021 (0–60 mg/kg, i.p.), followed 10–12 min later with NBQX (0–40 mg/kg, i.p.). Mice received a normally convulsive dose of cocaine (60 mg/kg, i.p.) 3–5 min later. The presence of some doses of NBQX improved the protective ability of ACEA-1021 alone. $^{*}P < 0.05$ compared to vehicle.

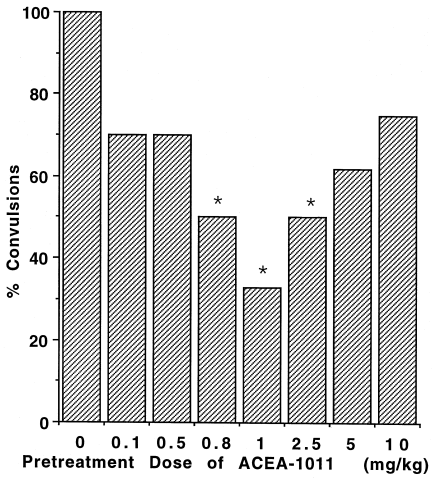

Fig. 2. Effects of the NMDA/non-NMDA receptor antagonist ACEA-1011 on the convulsive effects of cocaine. Mice were pre-treated with a dose of ACEA-1011 (0–10 mg/kg, i.p.), followed 15 min later with a convulsive dose of cocaine (60 mg/kg, i.p.). ACEA-1011 produced a significant attenuation of cocaine-induced convulsions. $^{*}P < 0.05$ compared to vehicle.

4. Discussion

In the present study, the highly selective AMPA/kainate receptor antagonists NBQX (Sheardown et al., 1990) and GYKI 52466 (Rogawski, 1993; Zormuski et al., 1993), were unable to significantly attenuate the convulsive and lethal effects of cocaine when administered alone. These negative findings involving non-NMDA receptor antagonists contrast with the ability of NMDA receptor antagonists to mitigate cocaine-induced convulsions and lethality (Rockhold et al., 1991; Witkin and Tortella, 1991; Matsumoto et al., 1997, 1998; Ushijima et al., 1998). However, our findings are consistent with reports that other non-NMDA glutamatergic antagonists, such as the glutamate release inhibitor riluzole and the metabotropic glutamate receptor antagonist L(+)-AP-3, fail to inhibit cocaine-induced convulsions and lethality in mice (Matsumoto et al., 1998; Pouw et al., 1998).

The inability of the AMPA/kainate receptor antagonists, NBQX and GYKI 52466, to attenuate cocaine-induced convulsions and lethality is neither a result of inadequate absorption of the drugs nor the testing of inappropriate doses. In the present study, NBQX and GYKI 52466 were administered under conditions that were

therapeutic in other animal models of seizure and cocaine-induced behaviors (Sheardown et al., 1990; Smith et al., 1991; Turski et al., 1992; Lallement et al., 1993; Bagetta et al., 1996). As compared to doses of NBQX previously used against cocaine-induced locomotor sensitization and self-administration, the doses employed in this study spanned the active ranges (Li et al., 1997; Jackson et al., 1998). In relation to seizures, NBQX has been reported to antagonize audiogenic seizures, pentylenetetrazol-induced kindling, and convulsions induced with picrotoxin, pentylenetetrazol, 3-mercaptoproprionate, and methyl-4-ethyl-6, 7-dimethoxy-9*H*-pyrido-(3,4-b)-indole-3-carboxylate with ED_{50}s of 40 mg/kg or less (Smith et al., 1991; Turski et al., 1992; Shimizu-Sasamata et al., 1996). Even after testing NBQX at the high 80 mg/kg, i.p. dose, however, our results show that it failed to attenuate the convulsive effects of cocaine, notwithstanding evidence of adequate absorption (e.g., reduced muscle tone). Similarly, GYKI 52466 has been reported to possess anticonvulsant actions against audiogenic seizures, maximal electroshock-induced seizures, amygdala kindling and convulsions induced by pentylenetetrazol, AMPA, kainate and 4-aminopyridine at doses that were comparable to those used in the present study (Chapman et al., 1991; Yamaguchi et al., 1993; Durmuller et al., 1994; Löscher and Honack, 1994). However, our results showed that GYKI 52466 completely failed to attenuate cocaine-induced convulsions, despite pronounced sedation in the animals. Therefore, when taken together, the data suggest that AMPA/kainate receptors are not the primary mediators of cocaine-induced convulsions, although they may play an important role in other types of seizures.

One might expect differences between AMPA/kainate vs. NMDA receptors to explain differences in the effectiveness of the antagonists in attenuating the convulsive and lethal effects of cocaine. However, areas of divergence between the two receptor subtypes are difficult to identify. NMDA receptors have an important and well-known role in neural, respiratory and cardiovascular control (Miyawaki et al., 1996; Aylwin et al., 1997; Rice and DeLorenzo, 1998), all of which are seriously compromised after a cocaine overdose. Although the role of AMPA/kainate receptors in these processes is less defined, they too appear to contribute to these systems (Miyawaki et al., 1996; Aylwin et al., 1997; Bongianni et al., 1998; Löscher, 1998). We also considered the possibility that convulsive doses of cocaine preferentially interact with areas of the brain enriched with NMDA receptors, as compared to AMPA/kainate receptors (Monaghan et al., 1989; Lee and Choi, 1992; Kohama et al., 1998). However, the overlapping distribution of NMDA and AMPA/kainate receptors in regions of the brain that underlie seizures, suggests that this is unlikely (Monaghan et al., 1989; Kohama et al., 1998). Therefore, the underlying reason for the inability of AMPA/kainate receptor antagonists to attenuate cocaine-induced convulsions and lethality is difficult to explain.

Although AMPA/kainate receptors do not appear to be primary mediators of the pathophysiological changes that occur after a cocaine overdose, they appear to be capable of influencing these processes indirectly. In the present study, the AMPA receptor antagonist NBQX failed to attenuate the convulsive effects of cocaine when administered alone, but it improved the protective ability of the NMDA receptor antagonist, ACEA-1021, when administered in combination. The addition of NBQX produced an approximate 2-fold shift in the protective ED_{50} for ACEA-1021. This finding is consistent with previous reports that NBQX can potentiate the neuroprotective and anticonvulsant properties of NMDA receptor antagonists in other animal and cell models (Zarnowski et al., 1993; Lippert et al., 1994).

The mixed NMDA/non-NMDA receptor compound ACEA-1011 also attenuated the convulsive effects of cocaine. When compared to the protective ED_{50} values elicited by related, but NMDA receptor preferring quinoxalinediones (e.g., ACEA-1021 48 mg/kg i.p.; ACEA-1031 7 mg/kg i.p.; ACEA-1328 15 mg/kg i.p.), ACEA-1011 had a lower protective ED_{50} (1 mg/kg, i.p.) than would be expected based on its potency at NMDA receptors alone. Because these compounds vary in their potencies and preferential affinities at the various glutamate receptor subtypes, it is difficult to conclusively evaluate the contribution of non-NMDA receptor activity alone in the protection against cocaine-induced convulsions. Qualitatively, however, ACEA-1011 has a 40-fold preference for NMDA receptors as compared to non-NMDA receptors (Woodward et al., 1995a), while the other ACEA compounds have up to a 500-fold better potency at NMDA receptors as compared to AMPA/kainate receptors (Woodward et al., 1995b). Therefore, it appears that antagonism of AMPA/kainate receptors enhances the protective effects through antagonism of NMDA receptors.

Despite ample evidence for an interaction between NMDA and non-NMDA receptors (Moore et al., 1995; Fedele and Raiteri, 1996), the nature of this interaction varies across systems. In some systems, NMDA and non-NMDA processes interact through networks of cells (Yu and Miller, 1996). In other instances, the two receptor types are co-localized on common nerve terminals, and the activation of non-NMDA receptors facilitates NMDA-mediated responses (Bekkers and Stevens, 1989). In particular, non-NMDA receptors facilitate the activation of NMDA receptors by allowing them to function under conditions in which they are normally prevented (e.g., magnesium blocking NMDA receptor activation) (Collingridge and Singer, 1990; Desce et al., 1992; Raiteri et al., 1992).

The specific mechanism(s) underlying the interaction between NMDA and non-NMDA receptors in the context of a cocaine overdose has yet to be determined. Nevertheless, the data reported herein strongly suggests that the interaction is complex, and probably occurs at both the

cellular and systems level. The co-localization of NMDA and non-NMDA receptors in regions of the brain that mediate seizures indicates that the potentiating effect of NBQX could be mediated through either cellular and/or network interactions. The shift in the dose curve for the protective effect of the NMDA antagonist ACEA-1021 in the presence of NBQX, however, was neither dose-dependent nor parallel, suggesting the existence of a physiological threshold of activation or a sequence of priming events for NBQX to fully express its effects. The complexity of these interactions is further affirmed by the loss of the protection provided by ACEA-1021 with the administration of higher doses of NBQX. These latter types of opposing actions most likely arise from interactions between networks of neurons because previous studies indicate that functional antagonism between NMDA and AMPA receptor antagonists are possible under in vivo conditions (Maj et al., 1995). When taken together with existing data demonstrating the involvement of multiple neurotransmitter systems (e.g., glutamate, serotonin, muscarinic, sigma, GABA, dopamine) in the convulsive effects of cocaine (Ritz and George, 1997; Ushijima et al., 1998), it is clear that further studies are needed to better understand the nature of these interactions.

In regards to the glutamatergic component, the data indicates the lack of a generalized overactivation of glutamatergic systems following a cocaine overdose. Therefore, while NMDA receptors can be targeted to alleviate the convulsive and lethal effects of cocaine, non-NMDA glutamate receptors appear to have a modulatory influence.

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