Changes in Seizure Susceptibility to Local Anesthetics by Repeated Administration of Cocaine and Nomifensine but Not GBR12935: Possible Involvement of Noradrenergic System

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Received March 24, 2000 Accepted April 28, 2000

ABSTRACT—We examined cross-sensitization of cocaine and synthetic local anesthetics to their seizure susceptibility after repeated administration. Seizure susceptibility of procaine and lidocaine increased after the end of two days of treatment with a subconvulsive dose of cocaine. Acute treatment with nomifensine but not GBR12935, a specific inhibitor of the dopamine transporter, facilitated lidocaine-induced convulsion. Furthermore, daily treatment with nomifensine for two days enhanced lidocaine-induced convulsion. These results suggest the possible involvement of the brain noradrenergic system in the changes in seizure susceptibility after repeated administration of some local anesthetics.

Keywords: Local anesthetic, Convulsion, Monoamine transporter

Cocaine has been shown to have convulsant effects, which were related to its local anesthetic action (1). In addition, the repeated, intermittent administration of cocaine to rodents can result in an increased susceptibility to cocaine-induced seizure (1). This phenomena was termed ‘cocaine kindling’, like other pharmacological kindling processes such as that induced by pentylenetetrazol. The local anesthetic lidocaine has been also found to induce kindling, as repeated administration of a subconvulsive dose of lidocaine increased the susceptibility to lidocaine-induced seizure (1). However, the time-course of its development differed from cocaine kindling.

There is evidence suggesting that cocaine inhibits the dopamine uptake system to exert psychostimulant action (2), while synthetic local anesthetics (LAs) have been believed to devoid of this effect. However, we have recently demonstrated that some LAs including procaine, but not lidocaine, display inhibitory action on monoamine transporters (3). This action was suggested to be related to the reported psychotomimetic action of some LAs (e.g., ref. 4). If cocaine kindling is related to or modified by its monoaminergic action, some LAs like procaine also show kindling that is similar to cocaine, and cross-sensitization occurs. Recently Shimamoto et al. (5) demonstrated that repeated administration of a subconvulsive dose of cocaine sensitized lidocaine-induced convulsion, whereas lidocaine

did not affect cocaine-induced convulsion. Taken together with our results on monoamine transporters (3), it is hypothesized that inhibitory action on monoamine transporter affects seizure susceptibility of some LAs, which may be interpreted as a different feature of cocaine- and lidocaine-induced kindling. To address this question, we examined cross-sensitization of cocaine and synthetic LAs to their seizure susceptibility after repeated administration.

Male ICR strain mice weighing from 20 to 30 g were used. All procedures and handling of animals were performed according to the guideline “Guiding Principles for the Care and Use of Laboratory Animals” approved by The Japanese Pharmacological Society as well as the guideline of Hiroshima University. The injection of drugs were performed between 2:00 PM and 5:00 PM to avoid the effects of circadian rhythms on these experiments. Animals had free access to food and water until 3 h before the experiments. Drugs were dissolved in saline and administered intraperitoneally at doses of 0.1 ml/10 g body weight. Equivalent volumes of vehicle were injected for control animals.

Mice were injected with convulsant and placed individually in an empty plastic cage for observation of seizure activity for 15 min. Seizure induced by lidocaine or procaine were characterized by symptoms of ataxia, short loss of the righting reflex and clonic convulsions. Seizures induced by cocaine were characterized by symptoms of increased locomotor activity, tail flick, jumping, loss of the

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righting reflex, and clonic and tonic convulsions. The former three symptoms, not observed in procaine or lidocaine treatment, may reflect the excitatory action of cocaine in the central nervous system. The percent of animals that exhibited convulsion in each treatment group were determined during 15 min after injection with LAs, as described previously (6, 7). The latency to the onset of convulsion induced by procaine, lidocaine and cocaine did not show any significant differences. The statistical analysis of significance of the differences in the incidence of convulsions was made by Fisher's exact probability test.

The effects of repeated administration of a subconvulsive dose of cocaine on susceptibility to seizures induced by a convulsive dose of cocaine, lidocaine or procaine was evaluated. Cocaine (30 mg/kg) or saline was administered daily via i.p. injection for 2 days. One day after the last injection, the cocaine- and saline-treated mice were challenged with cocaine (44 mg/kg), lidocaine (55 mg/kg) or procaine (140 mg/kg). To assess further the cross-sensitization, lidocaine (40 mg/kg) or procaine (120 mg/kg) was administered daily via i.p. injection for 2 days; and one day after the last injection, the convulsant dose of cocaine (44 mg/kg), lidocaine (55 mg/kg) or procaine (140 mg/kg) was injected.

Lidocaine and procaine causes dose-dependent induction of seizure activity (6, 7), like cocaine. We chose the subconvulsive dose of 40 mg/kg lidocaine, 120 mg/kg procaine and 30 mg/kg cocaine for daily treatment, and doses of 55 mg/kg lidocaine, 140 mg/kg procaine and 44 mg/kg cocaine that produced 10–30% incidence of seizure. Two days pretreatment with a subconvulsive dose of cocaine did not affect subsequent cocaine-induced seizure, but it significantly enhanced lidocaine- and procaine-induced seizure (Table 1). Daily treatment with a higher dose of cocaine (40 mg/kg), which did not induce convulsion at day 1, increased seizure occurrence at day 2 and day 3 (data not shown). Therefore, these results suggest that cocaine sensitized seizure activity induced by these LAs. Contrary to this, pretreatment with lidocaine did not affect seizure induced by subsequent administration of lidocaine, procaine or cocaine (Table 1). Procaine pretreatment had a tendency

to sensitize seizure induced by these LAs, although it was not statistically significant (Table 1). These results suggest that increase in seizure susceptibility to LAs produced by cocaine is not related to its local anesthetic action, but rather may be due to its inhibitory action on monoamine uptake. Post and Weiss (1) observed the lidocaine- as well as cocaine-induced kindled seizure, suggesting that both action is substantially due to their local anesthetic action. Pharmacogenetic analysis using different mice strains by Marley et al. (8) demonstrating the cross-sensitization/tolerance between cocaine and lidocaine also suggest that local anesthetic properties of cocaine appears to be responsible for its epileptogenic property. However, the time-course of the development of sensitization to the convulsant effect of cocaine and lidocaine was different; cocaine produces kindling after one or two days treatment, while lidocaine requires continuous treatment for 5–8 days to develop kindled seizure (1, 8). Therefore, it is conceivable that the difference results from, at least in part, cocaine's inhibitory action on monoamine uptake which lidocaine lacks (3). In the present study, as reported by Shimosato et al. (5), pretreatment with cocaine was found to elicit sensitization of both cocaine- and lidocaine-induced seizure, but pretreatment with lidocaine affected seizure susceptibility neither to cocaine nor to lidocaine. Taken together, these results suggest the possibility that seizure susceptibility to LAs might be modified by the intermittent elevation of monoaminergic activity through the inhibition of the uptake system, such as by the repeated treatment with cocaine. Tendency of procaine pretreatment to sensitize LAs-induced seizure may be related to its inhibitory action on monoamine transporters while lidocaine had no effect (3). We are currently investigating this possibility by using other synthetic LAs which displayed more potent inhibition of monoamine transporters than procaine (3).

We have previously demonstrated that the inhibition of GABAergic function by LAs contributes to their convulsive action (9, 10). Furthermore, the acute treatments to produce the stimulation of adrenergic neuronal activity facilitated the LAs-induced convulsions, while those for suppression decreased the convulsions, suggesting the invol-

Table 1. Effects of daily treatments with cocaine, procaine or lidocaine on seizure susceptibility induced by cocaine, procaine or lidocaine

Pretreatment	Challenge (% animals with convulsion)								
	Cocaine			Procaine			Lidocaine		
	%	N	P	%	N	P	%	N	P
Saline	20.8	24	—	12.5	32	—	22.5	40	—
Cocaine	26.1	23	0.7400	41.7	24	0.0268	50.0	32	0.0243
Procaine	26.7	15	0.7110	17.4	23	0.7071	29.2	24	0.5653
Lidocaine	18.8	16	>0.9999	12.5	24	>0.9999	18.2	22	0.7562

N: number of animals, P: probability by Fisher's exact P test.

Fig. 1. Effects of acute and chronic treatment with nomifensine on seizure activity induced by lidocaine. Nomifensine (5 mg/kg, i.p.) was administered 30 min before lidocaine (55 mg/kg, i.p.) for evaluation of its acute effect on lidocaine-induced convulsion (A). For assessment of the effect of chronic treatment with nomifensine, nomifensine (5 mg/kg, i.p.) was administered daily for 2 days, and then one day after the last injection the mice were challenged with lidocaine (55 mg/kg, i.p.) (B). Values represent % animals with convulsion. Number in the parenthesis is the number of animals tested. * $P < 0.05$, ** $P < 0.005$ vs saline-injected control animal.

vement of the adrenergic nervous system in the modification of LAs-induced convulsion (6). Since cocaine inhibits the uptake systems for both noradrenaline and dopamine, a question arises about which is associated with the effect of daily treatment with cocaine. To address this question, we used nomifensine that specifically inhibits uptake of noradrenaline and dopamine (11), and GBR12935 (1-[2-(diphenylmethoxy)ethyl]-4-(3-phenylpropyl)-piperazine), a specific inhibitor of the dopamine transporter (12). The doses of nomifensine and GBR12935 used in the present study are known to produce effectively the inhibition of noradrenaline and dopamine uptake in vivo, respectively (11, 12). Mice treated with nomifensine 30 min before injection of lidocaine showed an increase in lidocaine-induced convulsion (Fig. 1A). On the other hand, pretreatment with GBR12935 (5 mg/kg, i.p.) 30 min prior to lidocaine (55 mg/kg, i.p.) injection had no effect on lidocaine-induced seizure; % animals with convulsions in saline- and GBR12935-treated groups were 22 ± 4 and 20 ± 2 , respectively. These results confirmed our previous observation (6) that increase in noradrenergic activity in the brain enhances the lidocaine-induced convulsion, and further suggest the possibility that increase in dopaminergic activity does not affect lidocaine-induced seizure. These results do not entirely exclude the correlation of the dopaminergic system to LAs-induced seizure, as Ciarlone (13) demonstrated that depletion of brain dopamine decreased the convulsant threshold of lidocaine and procaine.

Two days pretreatment with nomifensine, like cocaine, produced an increase in seizure susceptibility to lidocaine (Fig. 1B). These results suggest that cocaine-induced cross-sensitization of seizure susceptibility to LAs is associated with its inhibitory action on monoamine uptake systems,

especially on noradrenaline transporter. Russell and Stripling (14) also suggested that cocaine's noradrenergic action may modulate kindled seizure expression via daily electrical stimulation of the left prepyriform cortex.

While extrapolation of the results obtained in mice to humans is hazardous, this study suggests potential clinical implications for the use of LAs which are frequently used in dental therapeutics. Most apparent is the possibility that patients being treated with antidepressants may have a degree of increment of the seizure susceptibility to LAs; thereby, we need caution to use LAs in such cases.

Acknowledgments

This work was supported in part by Grants-in Aid from the Japanese Ministry of Education, Science, Sports and Culture.

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