

NEUROCHEMICAL AND PHARMACOLOGICAL ASPECTS OF COCAINE-INDUCED SEIZURES

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Seizures associated with cocaine intoxication are serious clinical problem requiring immediate and adequate treatment, however their mechanism has not been fully elucidated. In contrast to early views, which convulsive properties of cocaine ascribed predominantly to the effect of this drug on voltage-dependent sodium channels, recent reports put much emphasis on the interaction of cocaine with GABAergic and glutamatergic systems. Accordingly, pharmacological studies demonstrated that cocaine-induced seizures were efficiently inhibited by GABA-A receptor agonists and NMDA receptor antagonists, whereas sodium and calcium channel blockers were ineffective. An involvement of serotonin 5-HT₂, dopamine and sigma receptors in cocaine-induced seizures has also been proposed. Furthermore, adaptive changes in various neuronal systems following cocaine-induced seizures has been vigorously investigated. Some of those changes, such as expression of immediate early genes and increase in neuropeptide biosynthesis may play a compensatory anticonvulsive role, however, other alterations e.g. up-regulation of NMDA receptors may increase susceptibility to seizures. This short review summarises recent advances in basic research on some neurochemical and pharmacological aspects of cocaine-induced seizures.

Key words: cocaine-induced seizures, GABA receptors, NMDA receptors, glutamatergic system

Clinical data indicate that cocaine has toxic effects on both cardiovascular and central nervous system (CNS). With respect to CNS, cocaine can induce stroke, intracranial hemorrhage, generalized seizures and exacerbate a preexisting seizure disorder [12, 24]. High doses of cocaine may also evoke seizures in a variety of animal species, whereas repeated subconvulsive doses of that drug induce kindling [27]. Among drugs which are known to aggravate cocaine-induced seizures are caffeine, morphine [8, 9] and tricyclic antidepressants [29], whereas corticosteroids and CRH facilitate cocaine-induced kindling [23].

Mechanism of seizures induced by cocaine is complex and involves interaction of the drug with several neurotransmitter systems as well as with voltage-dependent sodium channels. Early reports suggested that proconvulsant effect of cocaine, shared with other local anesthetics, was related to the inhibition of the voltage-dependent sodium channel and inhibitory pathways in the cortex and hippocampus [11]. However, a blocker of voltage-dependent sodium channels, phenytoin, shows little activity against cocaine-induced seizures [8] and other functional antagonists of both Na^+ and Ca^{2+} channels are generally ineffective [14]. In respect to calcium channels, these data are in agreement with reports which showed that calcium channel antagonists nifedipine and nimodipine had no effect on seizures and mortality following cocaine administration in rats [10, 40]. Other authors reported that nimodipine, nitrendipine and diltiazem inhibited cocaine-induced stereotypy but enhanced cocaine-induced seizures [2].

Cocaine enhances monoamine system activity through the blockade of dopamine and serotonin reuptake. Stimulation of dopamine D_1 receptors facilitates cocaine-induced seizures, whereas D_1 receptor antagonists inhibit cocaine (but not lidocaine)-induced lethality in stereoselective manner. Neither agonists nor antagonists of D_2 dopamine receptors affect cocaine-induced seizures [43], although Ushijima et al. found that D_2 receptor agonist, bromocriptine, inhibited convulsions evoked by intravenous infusion of cocaine in mice [41]. O'Dell et al. postulated that cocaine-induced convulsions appeared to be mediated by serotonin neurotransmission, acting primarily at 5-HT_2 receptors [30]. Cocaine-induced convulsions are blocked by the 5-HT_2 antagonists, cinanserin, ketanserin, and pirenperone, whereas stimulation or inhibition of 5-HT_1 receptors was without effects. Furthermore,

some antidepressants which are selective serotonin reuptake inhibitors facilitate cocaine-induced convulsions but not lethality, whereas dopamine reuptake inhibitors act in opposite way [29]. Finally, a significant difference has been found in 5-HT_2 receptor densities in discrete brain areas of two strain of mice C57BL/6J and C57BL/6ByJ, which are characterized by nearly two-fold difference in sensitivity to cocaine-induced convulsions [31]. Noradrenergic mechanism appears to be also involved in the regulation of cocaine-induced seizures. Propranolol, a β -receptor antagonist, and yohimbine, α_2 -receptor antagonists, enhance cocaine-induced seizures and lethality. On the other hand, clonidine, α_2 -agonist, and prazosin, α_1 -antagonists, suppress convulsive effects of cocaine. This indicates that the stimulation of α_1 - and α_2 -receptors facilitates and inhibits the cocaine-induced seizures, respectively [7, 40]. Increasing body of evidence points to an involvement of α receptors in cocaine-induced seizures [35] and it appears that the stimulation of α_1 receptors facilitates this process [26, 39].

Recent data indicate that inhibition mediated by γ -aminobutyric acid is a major target for the central action of cocaine, which can result in seizures. Electrophysiological study in freshly isolated rat hippocampal neurons showed that cocaine at high micromolar concentrations non-competitively depressed GABA current in the absence and presence of tetrodotoxin, indicating that this effect was not mediated through voltage-dependent sodium channels [44, 45]. With respect to inhibitory amino acids, action of cocaine seems not to be restricted to GABA-A receptors, since it also decreases the glycine-induced chloride ion current in hippocampal neurons [34]. Pharmacological studies showed [8, 13, 14] a significant protection against cocaine seizures in rats after the treatment with diazepam, phenobarbital and SKF-1000330A, an inhibitor of GABA uptake. Other positive modulators of GABA-A receptor such as some neurosteroids and chlormethiazole protected mice against acute cocaine-induced seizures and lethality and suppressed cocaine-induced kindling [13, 15]. More recently, Gaşior et al. [14] evaluated the efficacy of newly approved and potential antiepileptic drugs in prevention of cocaine-induced seizures. They found, that drugs that enhance GABA-mediated neuronal inhibition in a manner distinct from barbiturates and benzodiazepines offered the best protective/behavioral side effect profile. This is in line with the report on efficiency of GABA transaminase anti-

sense oligodeoxynucleotide in modulating cocaine-induced seizures in mice [1].

Glutamatergic system appears to play an important role in the mechanism of cocaine-induced seizures. Both competitive and noncompetitive NMDA antagonists inhibit cocaine-induced kindling, seizures and lethality [4, 8, 21, 22, 25, 36, 42]. On the other hand, positive modulators of NMDA receptors, polyamines, aggravate cocaine seizures [37]. Another regulator of NMDA receptor activity, nitric oxide, also modulates cocaine seizures. Some inhibitors of nitric oxide synthase, L-NAME and NOArg, inhibit the cocaine-induced kindling and mortality in mice, whereas 7-nitroindazole attenuates cocaine kindling but not acute cocaine-induced seizures [18, 19]. Moreover, inhibition of nitric oxide pathway prevents not only behavioral changes but also cocaine seizure-related increase in hippocampal proenkephalin gene expression in mice [33]. Antagonists of AMPA receptors are less effective than NMDA ones in attenuating cocaine seizures but they enhance anticonvulsant effects of NMDA antagonists [3, 32], whereas an inhibitor of glutamate release, riluzole, seems to be inactive. Cocaine-induced kindling is associated with elevated NMDA receptor binding in the striatum, amygdala and hippocampus and enhanced polyamine brain levels, and importance of these changes in sensitization to the toxic effects of cocaine has been suggested [20, 21, 38]. A role of metabotropic glutamate receptors in cocaine-induced seizures is still unknown, however, recent data have shown that cocaine-induced seizures alter the sensitivity of group II and III metabotropic glutamate receptors in the central amygdala [28]. With respect to other biochemical adaptive changes to cocaine seizures, which can be linked with the activation of NMDA receptors, one should mention a robust induction of immediate early genes (cFOS, zif 268) and neuropeptide genes such as proenkephalin, prodynorphin and neuropeptide Y in the hippocampal formation [6, 16, 17]. Since neuropeptide Y and dynorphin act as endogenous anticonvulsants, an increase in their biosynthesis may be regarded as a compensatory response of the central nervous system to convulsive effects of cocaine. On the other hand, stimulation of proenkephalin neurons, especially in the hippocampus, may aggravate the convulsive properties of cocaine *via* disinhibition of GABAergic interneurons. Such assumption is supported by pharmacological data which showed that antagonists of

mu and delta opioid receptors block cocaine-induced sensitization to seizures and death [5].

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