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Case Report

Shared vulnerability between seizures and psychosis in cocaine addiction?

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ABSTRACT

Cocaine-induced seizures (CIS) and cocaine-induced psychosis (CIP) may be complications of acute cocaine intoxication. CIS could result from a kindling process, involving the glutamate NMDA receptor (NMDAR) phosphorylation state, which is enhanced by activation of the dopamine D1 receptor (D1R). CIP is considered to be more specifically associated with the activity of the dopamine D2 receptor (D2R). The authors describe the case of a 21-year-old woman who presented with recurrent CIP during a period of increased cocaine abuse that ended in two consecutive CIS. This case report may illustrate a possible overlap in the mechanisms underlying CIS and CIP, disclosing some subtle interactions occurring between dopaminergic and glutamatergic receptors during cocaine chronic intoxication. Chronic cocaine exposure usually induces the formation of a NMDAR–D2R complex, which seems to be linked to the usual clinical effects of the drug, but also causes complex formation not to occur in both D2R-based CIP and D1R-based CIS. To explain the case of this patient, we propose a pharmacological hypothesis based on a literature review and implying the lack of formation of this complex, which triggers CIP and CIS. On a more practical level, this case report also encourages practitioners to be aware of the possible co-occurrence of CIP and CIS in cocaine abusers, especially with respect to antipsychotic medications that could be administered in such situations.

1. Introduction

Both seizure [1] and psychosis [2] may be complications of acute cocaine intoxication. Cocaine-induced seizures (CIS) could result from a kindling process, clinical examples of which have previously been reported [3]. Recent experimental data suggest the involvement of glutamate NMDA receptors (NMDAR) in this kindling process [4]. A possible role for the dopaminergic system in CIS has also been mentioned, as activation of dopamine D1 receptors (D1R) seems to enhance CIS, whereas activation of D2 receptors (D2R) experimentally inhibits CIS [5].

Furthermore, cocaine-induced psychosis (CIP) is likely associated with some pharmacogenetic aspects of the dopaminergic system, notably involving dopamine D2 receptors (D2R) [6]. We report here the case of severe and recurrent CIP foregoing inaugural CIS, which could possibly illustrate a vulnerability common to CIS and CIP that could be matched to complex interrelationships between dopaminergic and glutamatergic neurotransmission pathways.

2. Case report

Miss W., a 21-year-old woman, has a history of anorexia nervosa throughout adolescence, which currently is stabilized. Since the age of 18, she has been consuming cocaine several times a week. She also reported occasional consumption of ecstasy and amphetamine. At the beginning of our involvement, Miss W. had significantly increased her cocaine consumption over a 3-month period, and was consuming on a daily basis. From this point, psychotic symptoms began to occur after each cocaine intake, and would decline in the following hours. The symptomatology essentially consisted of feelings of persecution, notably with the recurrent sensation of being watched or followed. She also reported experiencing auditory verbal hallucinations at least twice. CIP was intermixed with more common symptoms of cocaine intoxication: irritability, hypervigilance, and psychomotor agitation. In response to this situation, the patient quickly tried changing her cocaine supplier, but this caused no change in symptomatology. During cocaine intoxication, she had a severe, first tonic–clonic seizure. She was hospitalized in the Department of Neurology, where she underwent EEG and MRI, but no abnormalities were found. She left the hospital and almost immediately relapsed into cocaine abuse, with reemerging CIP. Just a few days later she had a new episode of CIS. Because of the systematic recurrence of CIP and CIS, she decided to stop

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cocaine consumption definitively and she currently remains abstinent, with total cessation of all neuropsychiatric symptoms.

3. Discussion

Clinically, Miss W. seems to have manifested a kind of progressive neuronal intolerance to cocaine, which resulted first in CIP and then in CIS. We assume that this process underlies some complex interactions between glutamatergic and dopaminergic pathways. It has long been hypothesized that cocaine's clinical effects are related to both neurotransmission systems [7]. Moreover, as mentioned in the Introduction, the involvement of these systems is also suspected in atypical symptoms of cocaine intoxication, like CIS and CIP.

Cocaine-induced seizures are supposed to be a consequence of NMDAR activity [4], whereas D1R and D2R oppositely influence the trigger of CIS [5]. The proconvulsant action of D1R may be linked to its ability to induce NMDAR phosphorylation. Cocaine enhances levels of synaptic dopamine, thus overstimulating D1R, which induces the activation of intracellular protein kinase A-Cα (PKA-Cα) [8]. Activation of PKA-Cα results in both direct and indirect NMDAR phosphorylation (Fig. 1) [8]. The NMDAR phosphorylation state has recently been shown to be closely related to the development of status epilepticus [9]. Activation of D1R by cocaine could thus lead, in some cases, to the phosphorylation of NMDAR, which induces CIS. In addition, it has been shown that D1R agonists can experimentally induce seizures [10]. On the contrary, D2R activation seems to inhibit the proepileptic effects of cocaine in mice [11]. Thus, during cocaine exposure, D2R could balance the proconvulsant effects of activated D1R. But D2R also seems to play a central role in the occurrence of CIP, as in most states of psychosis [12]. So, why do only some cocaine users manifest CIP and CIS, and how is it possible to explain the case of mixed CIS and CIP in Miss W.?

It has recently been reported that cocaine's action leads to formation of the D2R–NMDAR complex [11]. This complex regulates NMDAR-mediated currents and inhibits NMDAR phosphorylation [11]. In the case of noncomplicated cocaine intoxication, CIS is prevented by the usual formation of this complex. In the case of Miss W., we hypothesize that for some reason, when the patient increased her consumption of cocaine, the NMDAR–D2R complex did not form at all or to only an insufficient extent. The uncomplexed D2R could thus have exerted uncommon clinical effects, particularly CIP, which is normally inhibited by formation of the NMDAR–D2R. Furthermore, the lack of NMDAR–D2R complex formation promoted NMDAR phosphorylation following cocaine-induced D1R activation. This mechanism triggered a proepileptic kindling process resulting in CIS.

Of course, confirmation of such a hypothesis requires more evidence, but we hope this hypothesis serves as inspiration for additional work.

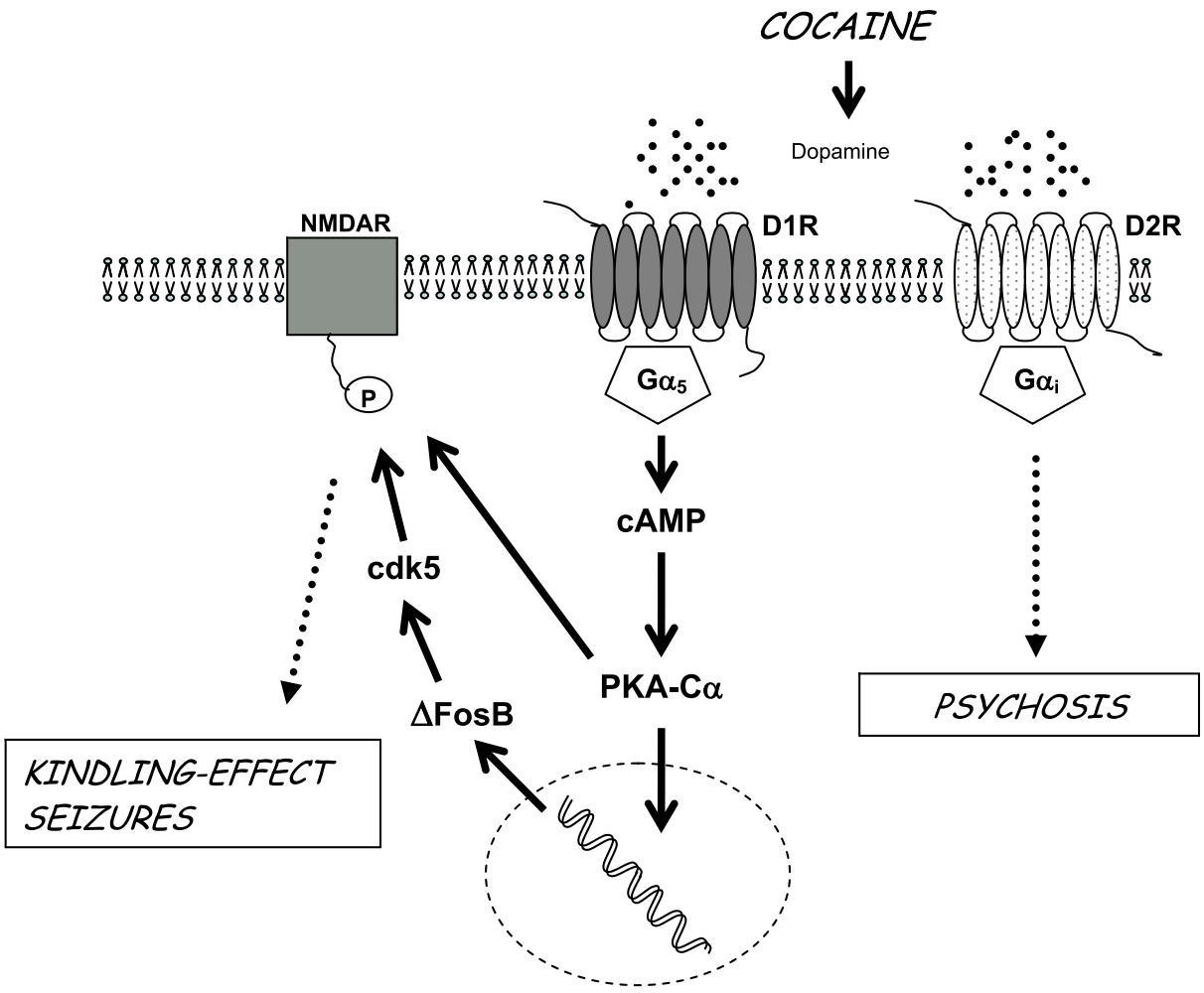

Fig. 1. Recurrent cocaine exposure activates D1R and D2R via dopamine's sustained action. Although stimulation of D2R is supposed to trigger the underlying neurobiological processes of psychosis, stimulation of D1R leads to a cascade activation via G-protein α_5 ($G\alpha_5$) and cyclic adenosine monophosphate (cAMP) to protein kinase A-Cα (PKA-Cα). Direct activation by PKA-Cα and the indirect delayed activation of cyclin-dependent kinase 5 (cdk5), via regulation of ΔFosB gene expression, result in phosphorylation of NMDA receptors (NMDAR). During cocaine intoxication, D2R and NMDAR form a complex that prevents NMDA phosphorylation (and then CIS), which could prevent isolated D2R from inducing CIP. In the case of Miss W., formation of the complex formation could have not occurred, resulting in enhancement of D1R-based NMDAR phosphorylation (promoting CIS), whereas the uncomplexed D2R could have led to CIP. Simplified schema inspired by Ron and Jurd [8].

If this hypothesis is proven, it would be interesting to learn why the NMDAR–D2R complex fails to form in some cocaine users. The reasons may involve genetics or epigenetics. Perhaps a certain percentage of cocaine users are particularly vulnerable to both CIP and CIS. Returning to clinical considerations, that is why we recommend that practitioners who care for cocaine users be alert to the possible co-occurrence of CIS and CIP when interviewing their patients. Perhaps the overlap in these two cocaine-induced complications has never been mentioned because it has not been sought in medical interviews.

Lastly, it seems important to consider medications that can or cannot be used by patients manifesting CIP or both CIP and CIS, as antipsychotics are known to induce EEG abnormalities that may lead to seizures [13]. Minimal data are available to allow comparison of the different drugs, but it seems that among all the antipsychotic drugs evaluated, quetiapine may be the one associated with the lowest risk of epilepsy, whereas clozapine and olanzapine are the most proconvulsant antipsychotics [13]. It is noteworthy that treatment of cocaine addiction with quetiapine has produced interesting preliminary results [14], whereas olanzapine has been reported to be ineffective [15]. So, all factors considered, and until further research proves otherwise, we suggest considering quetiapine the most relevant and safest antipsychotic treatment for cocaine users, especially those presenting with CIP. On the contrary, we recommend avoiding olanzapine and clozapine for treatment of CIP.

4. Conclusion

This case may illustrate a central psychopharmacological mode of action of cocaine that malfunctioned and led to both CIP and CIS in our patient. Confirmation of our hypothesis requires additional studies that investigate in greater depth the role of the NMDAR–D2R complex in the expression of cocaine-induced clinical effects. In a more pragmatic way, it also encourages practitioners to routinely ask cocaine users about the occurrence of CIS and CIP, to be aware of their possible co-occurrence, and to realize that such cases require care in the choice of therapeutics.

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