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ORIGINAL PAPER

Imbalance Between Nitric Oxide and Dopamine May Underly Aggression in Acute Neurological Patients

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Abstract The neurochemical basis of aggressive behavior in humans is not fully understood. In this study we explored the relationship between aggressiveness (as measured by the Overt Aggression Scale), cognitive performance (as measured by the Mini Mental State Examination), and biochemical markers of dopamine neurotransmission (homovanillic acid, HVA) and nitric oxide synthesis (nitrite plus nitrate, NO_x) in cerebrospinal fluid from 70 patients with acute brain disorders, mainly brain infections. Aggressive behavior and cognitive performance showed an inverse correlation. NO_x/HVA ratio was inversely correlated to aggressive behavior, and positively correlated to cognitive performance. A subanalysis with antipsychotic-naïve patients confirmed those results. The balance between nitric oxide and dopamine could be related to the cognitive control of aggressive impulse.

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Introduction

Aggressiveness is a relevant problem in the medical, social and legal frameworks. It may be present both in psychiatric and neurological patients. Several limbic and paralimbic structures, as amygdale and orbitofrontal cortex, are involved in the control of aggressive behaviors. Patients with traumatic or neoplasic lesions in the ventromedial and orbital prefrontal cortex may exhibit aggression [1], as well as acute brain infections, which are related to more diffuse cerebral dysfunction [2]. Also, a high percentage of patients with cognitive disorders may exhibit aggressive behavior, as those with a dementia diagnosis, suggesting an inverse relationship between cognitive performance and aggressive behavior [3]. Although aggression is common in patients with nervous system disorders, the neurochemical basis of aggressiveness is largely unknown.

The nitric oxide (NO) pathway may participate in the control of impulsive behaviors as aggression to others and self-aggression [4]. Neuronal NO synthase (nNOS) knock-out mice show aggressive behavior [5, 6], and pharmacological nNOS inhibition leads to the same effect [7]. Aggressive hamsters show few nNOS immunopossitive cells in the amygdala [8]. Furthermore, nNOS polymorphisms that lead to reduced gene transcription have been associated to aggressive behavior in humans [9]. As known, NO pathway is also related to cognitive function; its function as retrograde messenger underlies many of the structural changes observed in the central nervous system during learning and memory process [10].

Also, dopamine hyperactivity may be related to psychomotor agitation and aggressive behavior observed in neuropsychiatric patients [2], and D2 receptor antagonists reduce aggressive behavior in humans [11, 12]. Basic studies also provide evidence supporting a relationship between hyperactivity of the dopamine system and the development of aggressive behavior: D2L receptor knockout mice show reduced offensive aggression [6], dopamine levels increase before, during and following aggressive fights in rodents [11], and dopamine stimulating drugs induce aggressive behavior [13].

Furthermore, reduced NO synthesis and enhanced dopamine neurotransmission may be related to each other. NOS inhibition increases dopamine release [14] and its turnover in several brain regions [15]. D2 receptor agonists reduce, while antagonists increase, NADPH (NOS) staining in the striatum and cortex [16]. This facts suggest that NO and dopamine systems may have reciprocal regulatory effects, which could also be related to the control of functional programs, for instance those behind the complex repertory of behaviors described as aggression, which involves changes in cognitive, emotional, motivational, motor and autonomic systems.

The analysis of both pathways in acute aggressive neurological patients has not been reported. It is possible that reduced NO synthesis and increased dopamine neurotransmission are involved in aggressive behavior; moreover, it is possible that the balance between both NO and dopamine, rather than a single dysfunctional system, is related to aggressive behavior.

The purpose of this study was to determine the relationship between cognitive performance, aggressive behavior and the cerebrospinal fluid (CSF) concentrations of homovanillic acid (HVA, the main dopamine metabolite) and nitrite plus nitrate (NO_x, the main markers of NO synthesis) as well as the relationship between those systems, in the context of acute neurological disease.

Methods

1. Design: We conducted an observational, transversal and analytic study, approved by the Institutional Review Board.

2. Patients: We included consecutive acute neurological inpatients attended during 2006–2008 at the National Institute of Neurology and Neurosurgery of Mexico, who received a diagnostic lumbar puncture as part of their standard clinical assessment to rule out acute brain infections. Samples were stored frozen (−80°C) until analyzed. The study was conducted with approval of the Institutional Committee and according to the declaration of Helsinki. Informed consent was obtained from patients, or from the main relative of patients who had clinically significant consciousness disturbances.

3. MEASURES: CSF NO_x concentration was determined by high-performace liquid chromatography (HPLC) coupled to UV spectrophotometry as previously reported by our group [17, 18]. Briefly, samples were thawed and filtered through 0.45 μm pore diameter nylon membranes and eluted using an isocratic pump (1200 Series, Agilent Technologies). The mobile phase consisted on a 5 mM octylamine solution (adjusted to pH 6.4 with diluted sulfuric acid) and was pumped at a flow rate of 1.2 ml/min. Aliquots of 50 μl of CSF were injected into a Lichrosorb C18 column (5 μm particle size, 250 × 4.6 mm i.d., Alltech). Signals were recorded at 228 nm and integrated with ChemStation A.10.02 software (Agilent Technologies). CSF HVA concentration was determined by HPLC with electrochemical detection as previously described [2]. Samples were collected in plastic tubes containing sodium metabisulfite. The day of analysis, CSF was thawed, filtered through nitrocellulose membranes as described above, and mixed with an equal volume of 0.4 M perchloric acid. Samples were injected to an isocratic pump (LC 250, Perkin Elmer) using a Rheodyne valve with a 20-μl loop. The mobile phase consisted on a potassium phosphate buffer (30 mM, pH 3.1) containing 2 mM sodium octyl sulfate and 1.6% EDTA with 20% HPLC-grade absolute methanol pumped at a flow rate of 0.8 ml/min. Signals were recorded with a 656 Metrohm Electrochemical detector (set at 800 mV, 1 nA) and integrated using a Turbochrom 4.10 software (Perkin Elmer). The limit of detection determined as a signal: noise ratio of 3:1 from 10 blank injections was 36 nM. Lower and upper limits of quantification were 150 and 7,500 nM, respectively; response is linear ($r = 0.999$) between both limits. Intra-assay variation is 1.49–6.2% at different concentration levels across the entire linearity interval.

Psychiatric diagnosis was done by means of clinical interview performed by a neuropsychiatrist, using DSM-IV criteria [19]. Aggressive behavior was measured using the Overt Aggression Scale (OAS) [20]; this instrument was translated to Spanish and validated in a previous study [21], with high levels of reliabity, as measured by an intraclass correlation coefficient of 0.96. In order to classify each patient as having or not aggressive behavior, we took into account an OAS total score of severity of "0" to conform the non-aggressive group, and scores ranging from 1 to 12 to conform the aggressive group, which means that these patients had at least mild forms of physical or verbal aggression against self, others, or objects. Also, the total score of severity was used as an ordinal variable for correlational analysis. Overall cognitive functioning was documented using the Mini Mental State Examination (MMSE) [22]. Lack of cooperation in patients with aggression, as

well as severe cognitive dysfunction in some patients, limited the use of more detailed cognitive assessment tools.

4. Data analysis: Descriptive statistics, as well as Pearson or Spearman correlation analyses were done, according to the variables distribution. As a complementary analysis, we classified all subjects as having or not having aggressive behavior, taking into account the median value of the OAS total score of severity. Comparison between groups was then achieved by means of chi-square test, *t*-tests or alternatively, Mann Whitney tests, according to the numerical variables distribution. The control of confounding variables (for instance, antipsychotic drugs) could not be achieved by means of multivariate analysis because of the sample size; instead, stratified sub-analysis were used to control the effect of such confounding variables.

Results

1. Sample characteristics: 70 neurological patients (36.5 ± 14.8 years old) were included. 37 were female (52%). 40 patients had brain infections, as follows: non-herpetic viral encephalitis ($n = 16$), CNS tuberculosis ($n = 6$), neurocysticercosis ($n = 5$), cryptococcosis ($n = 5$), bacterial meningitis ($n = 5$), others ($n = 3$), and 30 patients with non-infectious acute neurological disease, mainly epilepsy ($n = 9$), cerebrovascular disease ($n = 6$), multiple sclerosis ($n = 2$), Miller Fisher syndrome ($n = 2$) and other disorders ($n = 11$).

2. Presence of aggressive behavior and relationship to other clinical variables: Aggressive behavior was present in 24 patients (34.3%) at the moment of clinical assessment. This behavior was not related to age or sex, although significant relationships were found between aggressive behavior and the diagnosis of brain infections ($p = 0.033$, chi-square test). Cognitive performance, as measured by the MMSE, was significantly different between aggressive and non-aggressive patients (22 ± 10 vs. 11 ± 8, $p < 0.001$, Mann Whitney test). No significant relationships were found between the presence of aggressive behavior and other clinical variables.

3. Presence of aggressive behavior and neurochemical markers: A comparison between aggressive and non-aggressive patients was achieved. There were no significant differences between these groups regarding age or CSF conventional measures, including opening pressure during lumbar puncture, number of cells, glucose or proteins concentrations. Figure 1 shows the comparative neurochemical analysis between patients with and without aggressiveness. As compared to the non-aggressive group, patients with aggressive behavior had a significant increase in HVA concentrations (231.26 ± 326.25 vs. 453.07 ± 367.89; $p = 0.012$, *t*-test), as well as a non-significant decrease in NO_x concentration (109.55 ± 95.86 vs. 89.57 ± 72.87; $p = 0.116$, *t*-test), and a significant decrease in the NO_x/HVA ratio (1616.47 ± 2153.12 vs. 548.90 ± 1141.85; $p = 0.001$, *t*-test).

As described before, brain infections were shown to be statistically related to aggressive behavior, so a sub-analysis was done to see the relationship between brain infections and the neurochemical markers. The comparison between patients with and without brain infections showed the following results: there was a significant increase in HVA concentrations related to infections (399.52 ± 408.01 vs. 184.36 ± 219.13, $p = 0.011$, *t*-test). We found no significant differences regarding the NO_x concentrations or the NO_x/HVA ratio.

4. Sub-analysis of antipsychotic naïve patients: A sub-analysis of antipsychotic naïve patients was conducted, taking into account the fact that these drugs may increase the dopamine metabolism and HVA concentrations [2]. As may been seen in Fig. 2, 47 patients were included in the sub-analysis. As compared to the non-aggressive group,

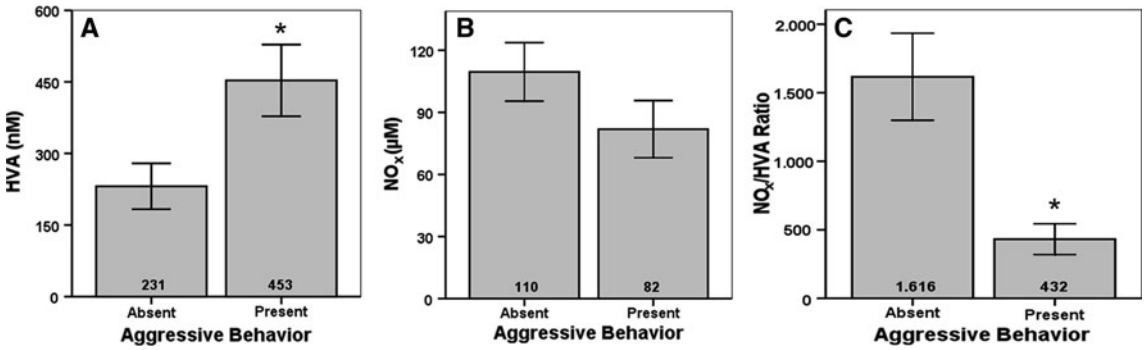

Fig. 1 Comparative analysis between neurological patients ($n = 70$) with and without aggressive behavior. **a** Patients with aggressive behavior had significantly higher concentrations of HVA ($p < 0.05$, *t*-test). **b** A non-significant decrease in NO_x concentration was found in patients with aggressive behavior. **c** A significant decrease in the NO_x/HVA ratio was found in patients with aggressive behavior ($p < 0.05$, *t*-test)

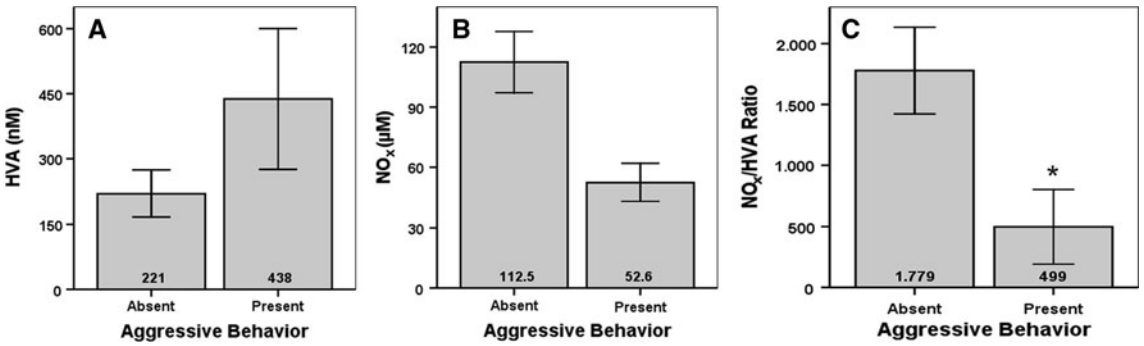

Fig. 2 Comparative analysis between antipsychotic-naïve neurological patients with aggressive behavior ($n = 7$) and without aggressive behavior ($n = 40$). **a** Patients with aggressive behavior had a non significant increase in HVA concentrations. **b** A non-significant decrease in NO_x concentration was found in patients with aggressive behavior. **c** A significant decrease in the NO_x/HVA ratio was found in patients with aggressive behavior ($p < 0.05$, *t*-test)

patients with aggressive behavior had an increase in HVA concentrations, although this increase was not statistically significant (220.63 ± 338.48 vs. 438 ± 429.63, $p = 0.134$, Mann Whitney test); this group had also a non-significant decrease in NO_x concentration (112.49 ± 96.52 vs. 52.63 ± 24.63, $p = 0.198$, Mann Whitney test). Regarding the NO_x/HVA ratio, the difference in this measure remained significantly different between groups (1778.88 ± 2257.17 vs. 498.78 ± 811.09, $p = 0.024$).

5. Correlation between neurochemical markers, aggressive behavior and cognitive performance. Table 1 shows correlations between the OAS total score of severity and several demographic, clinical and neurochemical markers. (a) TOTAL SAMPLE ($n = 70$). Significant correlations (at the $p < 0.05$ level) include: MMSE ($r = -.504$), HVA ($r = 0.388$) and NO_x/HVA ratio ($r = -0.437$). There was no significant correlation between NO_x, HVA, or NO_x/HVA to age or CSF cells, proteins or glucose. Cognitive performance, on the other hand, was related to HVA concentrations ($r = -.439$, $p = 0.001$, Spearman test), and the NO_x/HVA ratio ($r = .478$, $p < 0.001$). (b) SUB-ANALYISIS OF DRUG-NAÏVE PATIENTS. A sample of neurological drug-naïve patients was analyzed ($n = 47$). The NO_x/HVA ratio was the only neurochemical variable that remained significantly correlated to the OAS total score ($r = -0.352$). MMSE remained significantly related to aggressiveness ($r = -.340$).

Discussion

The results of the present study support the hypothesis of an imbalance between the nitric oxide and the dopamine system as underlying mechanisms participating in the genesis of aggressive behavior, in the context of acute neurological disease.

Aggression is a term that summarizes a varied repertory of behaviors intended to inflict harm [23]. Our results suggest that the occurrence of aggression is closely related to acute cognitive dysfunction. Several neuropsychological disturbances have been proposed as key components in the genesis of aggressive behavior: enhanced impulsivity and impaired recognition of social cues [23], as well as altered processing of risk under conditions of uncertainty,

Table 1 Correlations between overt aggression total score and cerebrospinal fluid (CSF) markers of dopamine and nitric oxide systems

Demographic, clinical and neurochemical variables	Neurological sample $N = 70$		Drug naïve neurological patients $N = 47$	
	R	*P*	*R*	*P*
Age (years)	.160	.188	.063	.678
Scholarship (years)	−.132	.287	−.053	.731
NO_x	−.148	.221	−.199	.180
HVA	**.388***	**.001**	.260	.078
NO_x/HVA ratio	**−.437***	**<.001**	**−.352***	**.015**
Pressure	.165	.178	.228	.132
Cells	.198	.102	−.118	.435
Proteins	−.010	.936	.038	.801
Glucose	−.053	.667	−.182	.227
MMSE	**−.504 ***	**<.001**	**−.340***	**.039**

Note: * Significant at the $p < 0.05$ level. Spearman correlation test was used

associated with disadvantageous decision making [24]. These mechanisms are both related to cortico-limbic connections and neurochemical signaling, which rely on dopamine and NO neurotransmitter systems.

As known, dopamine neurotransmission is associated to aggressiveness in mice [25]. Our results suggest that dopaminergic stimulation could also be involved in aggressive behavior displayed by acute neurological patients. However, antipsychotic treatment may alter dopamine metabolism as reflected in CSF measures [2], and hence may confound results interpretation. The correlation between aggressive behavior and the dopamine metabolite was not confirmed in drug-naïve patients from our study, suggesting that dopamine itself may not be the only underlying mechanism for aggression, although these results await confirmation in a larger sample.

In regard to the relationship of dopamine with other neurotransmitters, in a sample of subjects with violent behavior such as murder, murder attempt, or sexual crimes, the ratio HVA/5-HIAA was associated positively to Psychopathy Check List-Revised (PCL-R) ratings suggesting that aggression could be related to both, increased dopamine turnover and disregulation of serotonin neurotransmission in this population with steady aggressive behavior. This fact makes us consider that in a persistent situation, as ocurrs in patients with psychopathy traits [26] both neurotransmitters are involved. Our study is composed of a sample of patients with an episode of aggressive behavior elicited by acute neurological and neuropsychiatric disorder. Furthermore, in the present study the CSF sample was taken recently to aggressive event to discard brain infections. This study reveals that dopamine alteration in aggressive behavior could also be related to nitric oxide, another important molecular messenger in brain.

As well, our results support previous evidence on a NO dysfunction in patients with neuropsychiatric disorders often presenting with aggressiveness, as occurs in adult attention-deficit/hyperactivity disorder, suicide attempters and criminal offenders [4], and schizophrenia [17]. Several lines of evidence link the NO system and the cognitive control of behavior. Genetic studies have associated NO synthesis to aggression, and both pharmacologic and molecular neuronal NO synthase inhibition display aggressive behavior in animal models [5]. Behavioral and expressional phenotyping of mice lacking the neuronal isoform of nitric oxide synthase (NOS-I), has shown that the most prominent feature in this model is cognitive impairment in spatial learning and memory, as assessed by the Water Maze test [27, 28]. Genetic studies support the hypothesis that NO modulates depressive and self-aggressive behaviors NOS-I and NOS-II gene variants have been found to be involved in suicidal behavior and aggression towards others [29]. Also, nNOS inhibition results in a phenotype that displays reduced social investigation and increased aggression [7]. In the present study, NO_x were inversely correlated to aggression severity as measured by OAS, although did not reach statistical significance.

However, in this study NO_x/HVA ratio was significantly correlated to the total severity score of the OAS, both in drug-naïve patients and in the total sample, suggesting that an imbalance between both systems may be related to aggressive behavior. This measure had the strongest correlation to OAS total score of severity, and the most marked difference between aggressive and non-aggressive patients. Also, it was the only measure that remained statistically significant controlling the confounding effect of antipsychotics. Dopamine hyperactivity might increase the emotional responses of amygdale to signals arising from the internal or external milieu of the organism, whereas a deficit in NO availability could diminish the cortical blood flow, as well as the glutamatergic transmission of cognitively relevant information from hippocampus and prefrontal cortex to subcortical structures.

Several studies have shown that NO modulates dopamine neurotransmission. NO synthase (NOS) inhibition increases dopamine release [14, 30] and turnover [15]. Dopamine D1 receptor stimulation, in turn, decreases neuronal NOS expression in the striatum [31]. Thus, our results suggest that even though both dopamine and NO signalling have been independently associated to aggressive behavior, imbalance between both systems may underlie this relationship. An increase in dopamine signaling, which could be triggered by brain infections, as our study suggests, taking into account the significant increase in HVA observed in this population (as compared to patients without brain infections), could have inhibitory effects in the nitric oxide neurotransmitter system; which could, in turn, be related to an increase of dopamine release.

The neuroanatomical context of neurochemical abnormalities is a relevant issue in order to understand the mechanisms of aggressive behavior. Some authors have characterized the functional basis of aggressiveness as a failure in interaction between specific regions of the prefrontal cortex and the temporal lobe amygdale. It has been found that reduced white matter integrity in right inferior frontal regions is associated with higher levels of aggression [32]. The orbitofrontal cortex also participates in impulse control. Altered processing of risk under conditions of uncertainty, associated with lateral orbitofrontal cortex dysfunction, is associated with disadvantageous decision making, as may occur in patients with self-aggression, aggressive behavior towards others, and drug abuse [24]. As known, Type II NADPH-d-positive neurons, which are a cortical source of nitric oxide, have a well defined distribution in the prefrontal cortex [33]. Regulatory polymorphisms

of NOS1 modulate prefrontal brain functioning [34], and NO signaling may act to amplify coherent corticostriatal transmission and synchronize striatal output [35].

In the context of psychiatry, patients with a schizophrenia diagnosis assessed by means of functional MRI studies showed significant reductions in functional connectivity between amygdala and ventral prefrontal regions. As known, NO signaling in the lateral nucleus of the amygdala is involved in gene expression related to fear memory consolidation [36]. Lower functional connectivity between amygdala and ventral prefrontal regions has been associated with higher levels of self-rated aggression [32]. The reciprocal regulatory effects of dopamine and nitric oxide in the transmission of neural signals from the basolateral limbic system to the fronto-subcortical system, could be of relevance to understand the onset of aggressive behavior in the context of acute neurological patients.

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