Focus on aggressive behaviour in mental illness

Fisiopatologia dei comportamenti aggressivi in salute mentale

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SUMMARY. Background. Aggression is a behaviour with evolutionary origins, but in today's society it is often both destructive and maladaptive. Increase of aggressive behaviour has been observed in a number of serious mental illnesses, and it represents a clinical challenge for mental healthcare provider. These phenomena can lead to harmful behaviours, including violence, thus representing a serious public health concern. Aggression is often a reason for psychiatric hospitalization, and it often leads to prolonged hospital stays, suffering by patients and their victims, and increased stigmatization. Moreover, it has an effect on healthcare use and costs in terms of longer length of stay, more readmissions and higher drug use. **Materials and methods.** In this review, based on a selective search of 2010-2016 pertinent literature on PubMed, we analyze and summarize information from original articles, reviews, and book chapters about aggression and psychiatric disorders, discussing neurobiological basis and therapy of aggressive behaviour. **Results.** A great challenge has been revealed regarding the neurobiology of aggression, and an integration of this body of knowledge will ultimately improve clinical diagnostics and therapeutic interventions. The great heterogeneity of aggressive behaviour still hampers our understanding of its causal mechanisms. Still, over the past years, the identification of specific subtypes of aggression has released possibilities for new and individualized treatment approaches. **Conclusions.** Neuroimaging studies may help to further elucidate the interrelationship between neurocognitive functioning, personality traits, and antisocial and violent behaviour. Recent studies point toward manipulable neurobehavioral targets and suggest that cognitive, pharmacological, neuromodulatory, and neurofeedback treatment approaches can be developed to ameliorate urgency and aggression in schizophrenia. These combined approaches could improve treatment efficacy. As current pharmacological and therapeutic interventions are effective but imperfect, new insights into the neurobiology of aggression will reveal novel avenues for treatment of this destructive and costly behaviour.

KEY WORDS: aggression, anger, emotions, impulsivity, violence.

RIASSUNTO. Introduzione. L'aggressività è un comportamento con origini evolutive, ma nella società di oggi è spesso distruttivo e disadattivo. Un aumento del comportamento aggressivo è presente in molte malattie mentali e rappresenta una sfida clinica per il servizio sanitario. Questi fenomeni possono portare ad agiti dannosi e violenti, rappresentando una grave preoccupazione per la salute pubblica. L'aggressività è spesso motivo di ospedalizzazione psichiatrica, e può portare a soggiorni ospedalieri prolungati, sofferenze dei pazienti e delle loro vittime con aumento della stigmatizzazione. Inoltre, ha un importante effetto sui costi della salute pubblica, in termini di lunghezza maggiore di permanenza, revolving-doors dei ricoveri e uso di sostanze d'abuso più frequente. **Materiali e metodi.** In questa rassegna, attraverso una ricerca selettiva della letteratura pertinente 2010-2016 condotta su PubMed, vengono analizzate e riassunte le informazioni provenienti da articoli originali, recensioni e capitoli di libri su aggressività e disturbi psichiatrici, discutendo la base neurobiologica e la terapia dei comportamenti aggressivi. **Risultati.** L'aumento e l'integrazione delle conoscenze sulla neurobiologia dell'aggressività sarà di sicura utilità per migliorare la diagnostica clinica e gli interventi terapeutici. La grande eterogeneità dei comportamenti aggressivi ostacola ancora la completa comprensione dei meccanismi causali. Tuttavia, negli ultimi anni, l'identificazione di specifici sottotipi di aggressività ha permesso lo sviluppo di nuovi approcci di trattamento individualizzati. **Conclusioni.** Studi di neuroimaging possono contribuire a chiarire ulteriormente la correlazione tra il funzionamento neurocognitivo, i tratti di personalità e il comportamento antisociale e violento. Recenti studi indicano l'esistenza di target neurocomportamentali modulabili, suggerendo così che approcci di trattamento cognitivo, farmacologico, neuromodulatorio e neurofeedback possono essere sviluppati per migliorare l'urgenza e l'aggressività nella schizofrenia. Questi approcci combinati potrebbero quindi migliorare l'efficacia del trattamento. Poiché gli interventi farmacologici e terapeutici attuali sono sì efficaci ma imperfetti, nuove intuizioni nella neurobiologia dell'aggressività riveleranno nuovi percorsi per il trattamento di questo comportamento umanamente distruttivo e costoso in termini di sanità.

PAROLE CHIAVE: aggressività, rabbia, emozioni, impulsività, violenza.

INTRODUCTION

Aggression is a behaviour with evolutionary origins, but is often both destructive and maladaptive in today's society. Increase of aggressive behaviour has been observed in a several of serious mental illnesses, and it represents a clinical challenge for mental healthcare provider. These phenomena can lead to harmful behaviours, including violence, and thus rep-

resent a serious public health concern[1]. Aggression is often a reason for psychiatric hospitalization, and it often leads to prolonged hospital stays, suffering by patients and their victims, and increased stigmatization. Moreover, it has an effect on healthcare use and costs in terms of longer length of stay, more readmissions and higher drug use[2].

A great challenge has been revealed regarding the neurobiology of aggression, and an integration of this body of knowledge will ultimately improve clinical diagnostics and therapeutic interventions.

In this review, based on a selective search on 2010-2016 pertinent literature, we analyse and summarize information from original articles, reviews, and book chapters about aggression and psychiatric disorders, discussing the neurobiological basis and therapy of aggressive behaviour.

NEUROBIOLOGICAL BASIS AND NEUROIMAGING EVIDENCE

Research over past decades has confirmed the involvement of neurotransmitter function in aggressive behaviour: mostly serotonin hypothesis[3], but also dopaminergic and vasopressinergic systems, glutamate, norepinephrine, γ-aminobutyric acid and cholecystokinin neuropeptide (CCK)[4] have been considered.

CCK is a neuropeptide that among others is apparently involved in the pathophysiology of psychiatric disorders. The excitatory role of CCK in negative affective emotions as well as in aversive reactions, antisocial behaviours and memories, has been indicated by numerous electrophysiological, neurochemical and behavioural methodologies on both animal models for anxiety and human studies. Experimental evidences suggest the role of CCK in the induction of aggressive behaviour[5].

Complex interaction among neurotransmitters occurs in brain areas and neural circuits such as the orbitoprefrontal cortex, anterior cortex, amygdala, hippocampus, periaqueductal gray, and septal nuclei, where receptors of these neurotransmitters are expressed. Neurobiological mechanism of aggression is important to understand the rationale for using atypical antipsychotics, anticonvulsants, and lithium in treating aggressive behaviour[6].

During the last decades neuroimaging researches on aggression have been developed. Data from these studies performed to date are extremely interesting. Frontal and temporal lobe abnormalities are found consistently involved in aggressive schizophrenia patients.

Radiological methods have shown reduced activity mostly in frontal and temporal regions. Functional MRI studies (fMRI) have provided controversy results, most of them finding reduced activity in inferior frontal and temporal regions. Few studies have demonstrated increased activity in other regions. Some fMRI studies found a negative association between violent behaviour and frontal and right-sided inferior parietal activity. Positron emission tomography and single photon-emission computed tomography (SPECT) data indicate deficits in the orbitofrontal and temporal cortex[7].

MRI brain volumetric measures did not show consistent results regarding volume of frontal structure[8].

Frontal and temporal abnormalities appear to be a reliable feature of aggression in schizophrenia, but their exact meaning is difficult to understand due to the heterogeneous nature of this behaviour.

Literature continues to grow, guided by pre-clinical research and supported by the implementation of increasingly sophisticated neuroimaging methodology. A more complex picture has emerged, focusing on regional volumes, functional studies, and interregional connectivity with significant emphasis on the amygdala and amygdala-frontal circuitry.

Aggression may be present across the spectrum of psychopathology, and underlies criminal antisocial behaviours. Human aggression is a complex and underspecified construct, making scientific discovery extremely complex. Nevertheless, some biologically tractable subtypes are evident, and one in particular – impulsive (reactive) aggression – appears to account for many features of aggression-related dysfunction in psychiatric illness. Impulsive-aggression is significantly heritable, suggesting genetic transmission. However, the specific neurobiological mechanisms that mediate genetic risk for impulsive-aggression remain unclear. Existing data on genetics and neurobiology of individual differences in impulsive-aggression behaviour, emphasize the particular role of genetic variation in Monoamine Oxidase A (MAOA) and its impact on serotonergic signalling within corticolimbic circuitry[9].

Human aggression/impulsivity-related traits have a complex background that is greatly influenced by genetic and non-genetic factors. Highly conserved brain regions including amygdala, which controls neural circuits triggering defensive, aggressive, or avoidant behavioural models regulate the relationship between aggression and anxiety. Dysfunction of neural circuits responsible for emotional control was shown to represent an etiological factor of violent behaviour. In addition to amygdala, these circuits also involve the anterior cingulated cortex and regions of the prefrontal cortex. Excessive reactivity in the amygdala associated with inadequate prefrontal regulation increase the likelihood of aggressive behaviour. Developmental alterations in prefrontal-subcortical circuitry as well as neuromodulatory and hormonal abnormality appear to play a major role. Imbalance in testosterone/serotonin and testosterone/cortisol ratios (e.g., increased testosterone levels and reduced cortisol levels) increases the propensity toward aggression because of reduced activation of the neural circuitry of impulse control and self-regulation. Serotonin facilitates prefrontal inhibition, and thus insufficient serotonergic activity can enhance aggression.

AGGRESSION AND GENETIC PATTERN

Genetic predisposition to aggression appears to be deeply affected by the polymorphic genetic variants of the serotoninergic system that influences serotonin levels in the central and peripheral nervous system. Biological effects of this hormone, rate of serotonin production, synaptic release and degradation are controlled by genetic polymorphism. Among these variants, functional polymorphisms in the MAOA and serotonin transporter (5-HTT) may be of particular importance due to the relationship between these polymorphic variants and anatomical changes in the limbic system of aggressive people. Furthermore, functional variants of MAOA and 5-HTT mediate the influence of environmental factors on aggression-related traits[10].

While genome-wide association studies are lacking, a number of candidate genes have been investigated[11]. Schizophrenia patients show an increased risk for aggression and violent behaviour, but the neurobiological basis and correlates of this risk have not been investigated. By far, the most intensively studied focus on the catechol-O-methyltransferase (COMT) gene on chromosome 22. COMT is involved in the metabolism of dopamine. Several studies suggest that the Val158Met polymorphism of this gene affects COMT activity. Methionine (Met)/Met homozygote schizophrenia patients show 4- to 5-fold lower COMT activity than valine (Val)/Val homozygotes, and some studies have found an association with aggression and violence. Recently, a new functional single-nucleotide polymorphism in the COMT gene, Ala72Ser, was found to be associated with aggressive behaviour in schizophrenia, but this finding warrants further replication[12].

Current evidence does not support the use of such genes to predict dangerousness or as markers for therapeutic interventions. Successful identification of associations between genetic markers and aggression would contribute to better understand the neurobiology of aggressive behaviour and potentially provide useful tools for risk prediction and therapeutic targets for high-risk groups of patients and offenders.

MENTAL ILLNESS AND CLINICAL PRACTICE

A modest association between certain types of mental illness and aggression has been demonstrated.

Aggression risk assessment is a process of identifying patients who are at greater risk of aggression in order to facilitate the timing and prioritisation of preventative interventions. Clinicians should base these risk assessments on empirical knowledge and consideration of case-specific factors to inform appropriate management interventions to reduce the identified risk[13]. Debate about the appropriateness of clinician involvement in aggression risk assessment is sometimes based on a misunderstanding about the central issues and degree to which this problem can be effectively managed. The central purpose of risk assessment is prevention rather than prediction of aggression.

Factors that were significantly associated with in-patient aggression included being younger, male sex, involuntary admissions, not being married, diagnosis of schizophrenia, greater number of previous admissions, history of violence, history of self-destructive behaviour and history of substance abuse. Comparing aggressive with non-aggressive patients, important differences between the two populations may be highlighted. These differences may help physicians predict which patients might become aggressive and therefore enable steps to be taken to reduce aggressive behaviour. However, the associations found between these actuarial factors and aggression was small. Dynamic factors such as a patient's current state and context of clinical practice need to be considered to reduce inpatient aggression[14].

On a psychological level, aggression in schizophrenia has been primarily attributed to psychotic symptoms, desires for instrumental gain, or impulsive responses to perceived personal slights. Often, multiple attributions can coexist during a single aggressive episode. Impulsivity appears to largely account for aggression in schizophrenia, especially in inpatient settings. It is elevated in several psychiatric disorders, and in schizophrenia, it has been related to aggression[15].

A higher risk of developing aggression has been demonstrated in schizophrenic patients with no other comorbidities. This risk is considerably increased by frequent comorbid antisocial personality disorder or psychopathy, as well as by comorbid substance use disorders. Conduct disorder and conduct disorder symptoms increase risk for aggressive behaviour in patients with schizophrenia. Aggression among adults with schizophrenia may follow at least two distinct pathways: one associated with premorbid conditions, including antisocial conduct, and another associated with the acute psychopathology of schizophrenia.

Aggressive behaviour in bipolar disorder occurs mainly during manic episodes, but it is more frequent in euthymic patients in comparison with controls. Risk of violent behaviour is increased by frequent comorbidities as borderline personality disorder, antisocial personality disorder, and substance use disorders. Borderline personality disorder and bipolar disorder are related in their phenomenology and response to medication. These two disorders share a tendency to impulsiveness, and impulsive behaviour, including impulsive aggression, is particularly expressed when they co-occur[16].

Moreover, current literature underlines high risk of aggression in borderline personality disorder (BPD) with factors that differentiate aggressive from non-aggressive individuals with BPD and could predict risk of aggression at an individual level. BPD does not appear to be independently associated with increased risk of violence in the general population. History of childhood maltreatment, violence or criminality, and comorbid psychopathy or antisocial personality disorder appears to be predictors of violence in patients with BPD[17].

Patients experiencing mental disorders show a high risk for developing aggressive behaviour throughout their lifetime[18]. During the past years the introduction of atypical antipsychotics and increased use of anticonvulsants and lithium has changed dramatically the treatment paradigm of aggressive patients. Critical reviews of clinical trials using atypical antipsychotics (aripiprazole, clozapine, loxapine, olanzapine, quetiapine, risperidone, ziprasidone, and amisulpride)[19], anticonvulsants (topiramate, valproate, lamotrigine, and gabapentin), and lithium are present in literature[20]. Given the complex, multifaceted nature of aggression, a multifunctional combined therapy, targeting different receptors, seems to be the best strategy. This approach is supported by translational studies and few human studies. Additional randomized, double-blind, clinical trials to confirm the clinical efficacy of this framework are needed[21,22].

Reducing the risk of violent and aggressive behaviour in patients with schizophrenia remains a clinical priority. Several studies have focused their attention on second-generation antipsychotic drugs.

Clozapine's anti-aggressive effect has been mainly explored in patients with schizophrenia, with less evidence available for other psychiatric disorders, including BPD, autistic spectrum disorders, post-traumatic stress disorder, bipolar disorder and learning disability. Although there are no conclusive evidences to address the question of whether or not clozapine is more effective than other antipsychotics[23], emerging results suggest that, it is successful in reducing risk of aggression in

patients with schizophrenia and might be the best treatment in selected patients. In schizophrenic patients, clozapine's anti-aggressive effect seems to be more marked in those with treatment-resistant illness. Its anti-aggressive properties appeared to be "specific", being to some extent greater than its general antipsychotic and sedative effects. It may offer an advantage over other antipsychotics, although mostly in case of traditionally defined "treatment resistance" or more broadly defined "complex cases" with comorbidity. Larger, randomized, blinded, controlled studies with robust characterization of participants, and standardized measures of violence and aggression are needed to fully understand this link and explore the exact mechanisms of action of this drug[24].

High quality studies accessing the efficacy of pharmacological agents other than anticonvulsants for the treatment of impulsive aggression are still missing[25].

Aggressive behaviour is a common phenomenon during childhood and adolescence, and at the same time it is an associated feature of many psychiatric disorders during this age. Persistent aggression is related to a variety of negative outcomes in adulthood, including low socioeconomic status and unemployment, criminal behaviour and social isolation[26]. Attention deficit hyperactivity disorder (ADHD) is often associated with symptoms of aggression in children and adolescents. Clinically, aggression can derive from hyperactivity and impulsivity, or could be a distinct symptom from a comorbid diagnosis.

Past researches have recommended treating first the primary disorder of ADHD rather than associated symptoms. Stimulants are the most common treatment for paediatric ADHD, which can be helpful in decreasing aggressive behaviours. Alpha-adrenergic agonists and atomoxetine are non-stimulant medications for ADHD and aggression, but more researches are needed to compare these drugs to stimulants. If aggressive symptoms do not improve with treating the primary disorder, aggression can be treated separately. Risperidone, lithium, valproic acid, clonidine, and guanfacine have shown positive results in reducing aggression, but these studies showed limitations[27].

Variability in treatment tolerance in patients has stimulated research in pharmacogenetics for ADHD. Although this field is still emerging, previous studies support a link between the response rate of methylphenidate and the dopamine transporter (DAT1) and an association between the metabolism rate ofatomoxetine and hepatic cytochrome 450 isozymes. Pharmacogenetics may be relevant to ADHD and associated aggression. Further research in pharmacogenetics will strive to identify patterns of genetic variations that can tailor individual treatments[28].

Agitation and aggression commonly arise in people with Alzheimer's disease and other dementias. These kind of behaviour are particularly distressing for patients, often confer risk to them and to others, as well as raising significant clinical challenges. Currently, the best approach for managing these symptoms is within a framework of good practice that promotes prevention, monitoring and the use of nonpharmacological alternatives, with judicious short- term use of antipsychotics, when appropriate. There is a growing body of literature supporting the use of nonpharmacological approaches as well as treatment of painas a first-line management strategy prior to psychopharmacotherapy. Antipsychotic medications are most commonly prescribed to address agitation and aggression. Evidences indicate this approach results in a modest but significant improvement in aggression in the short term (6-12 weeks) although the impact on other symptoms of agitation is limited. Weak evidences support their use in longer term, where prescriptions of more than 12 weeks and longer periods are associated with cumulative risk of severe adverse events. Suggested pharmacological alternatives with most promising preliminary evidence include memantine, carbamazepine, citalopram, and prazosin, but none of these agents have sufficient confirmation in treating agitation and aggression to recommend their use in routine clinical practice[29].

Alcohol-related aggression, a longstanding, serious, and pervasive social problem, has provided researchers from different disciplines with a model to study individual differences in aggressive and violent behaviour[30]. Alcohol-related aggression and violence are a widespread cause of personal suffering with high socioeconomic costs. Clearly not all alcohol consumers will become aggressive after drinking and similarly, not all individuals with alcohol use disorders will exhibit such untoward behaviour. Rather, the relationship is best conceptualized as complex and indirect and is influenced by a constellation of social, cognitive, and biological factors that differ greatly from one person to the other. The link between alcohol consumption and aggression arise by various interacting factors. Aggression is promoted both by the cognitive deficits occurring in connection with acute or chronic alcohol use and, by prior experience of violence. Only a minority of persons who drink alcohol become aggressive. On the other hand, alcohol abuse and dependence together constitute a commonly diagnosed cause of suicide. Current research indicates that the individual tendency toward alcohol-induced aggression depends not just on neurobiological factors, but also on personal expectations of the effects of alcohol, on prior experience of violent conflicts, and on the environmental conditions of early childhood, especially social exclusion and discrimination[31].

Potential therapeutic approaches involve reinforcing cognitive processes or pharmacologically modulating serotonergic neurotransmission. The rich body of literature on alcohol-related aggression allowed the identification of several potential high-yield targets for clinical intervention: cognitive training for executive dysfunction, and psychopharmacology targeting affect and threat perception, which may also generalize to other psychiatric conditions characterized by aggressive behaviour[32].

Clinical observations suggest that sleep problems may be a causal factor in the development of reactive aggression. Although limited in number, some studies suggest that treatment of sleep disturbances reduces aggressiveness and problematic behaviour, irritability, and hostility. In line with this, sleep deprivation actually increases aggressive behaviour in animals and angriness, short-temperedness, and the outward expression of aggressive impulses in humans. In most people poor sleep will not evoke actual physical aggression, but certain individuals, such as forensic psychiatric patients, may be particularly vulnerable to the emotional dysregulating effects of sleep disturbances.

The relation between sleep problems and aggression may be mediated by the negative effect of sleep loss on prefrontal cortical functioning. This most likely contributes to loss of control over emotions, including loss of the regulation of ag-

gressive impulses to context-appropriate behaviour. Other potential contributing mechanisms connecting sleep problems to aggression are most likely found within the central serotonergic and the hypothalamic-pituitary-adrenal-axis. Individual variation within these neurobiological systems may be responsible for amplified aggressive responses induced by sleep loss in certain individuals. Identify the individuals at risk is fundamental, since recognition and adequate treatment of their sleep problems may reduce aggressive and violent incidents[33].

CONCLUSIONS

The great heterogeneity of aggressive behaviour still hampers our understanding of causal mechanisms. Still, over the past years, the identification of specific subtypes of aggression has opened possibilities for new and individualized treatment approaches.

Neuroimaging studies may help further elucidate the interrelationship between neurocognitive functioning, personality traits, and antisocial and violent behaviour.

Recent studies point toward manipulable neurobehavioral targets and suggest that cognitive, pharmacological, neuromodulatory, and neurofeedback treatment approaches can be developed to ameliorate urgency and aggression in schizophrenia. It is hoped that these approaches will improve treatment efficacy.

As current pharmacological and therapeutic interventions are effective but imperfect, new insights into the neurobiology of aggression will reveal novel opportunities for treatment of this destructive and costly behaviour.

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