

Neuropharmacology of Aggressive Behavior: Serotonergic Medications, Mood Stabilizers and Antipsychotics

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Abstract

Aggression has been recognized as a near-universal behavior with substantial influence on human and animal social systems. It can be a significant problem since escalated aggression may result in serious damage to others and can reveal itself as a symptom of psycho-pathologies. It is often considered to be the product of environmental stressors, health problems, pain, psychiatric morbidity or behavioral stressors. This article aims to review and discuss the advancements of neuropharmacological agents related to aggression. An imbalance in neurochemicals is thought to be the primary reason for psychological problems and seizure activity. The understanding of each neurotransmitter's functions and responsibilities explains why a decrease or increase in normal levels would cause elevated aggression. Psychopharmacology is one of the fields of medicine that addresses the use of medications to correct or alleviate common mental illnesses. It is a scientific discipline that utilizes drugs to increase our knowledge and understanding of the workings of the mind. It emphasizes drug induced changes in mood, thinking, and behavior. Among its aim is the utilization of medicinal substances for the restoration and maintenance of mental health, the prevention of mental breakdowns, and the exploration of the reaches of the mind. Its basic purpose is to help disease, but to change the personality, improve human nature, or cure bad habits. Developing novel therapies to reduce or prevent violent outbursts is a key objective of psychopharmacological research on aggression. Despite considerable progress, therapeutic possibilities for controlling or coping with, pathological aggressive behavior remain far from being satisfactory. Consequently, studying both the fundamental causes of aggression and dysfunctions and the modification of behavior by pharmacologic interventions is surmountable.

Keywords: *Aggressive Behavior; Serotonergic Medications; Mood Stabilizers and Antipsychotic*

Introduction

Aggressive behavior has been accepted as a universal problem with significant influence on both human and animal social systems [1,2]. The propensity for aggression exists whenever the need of two or more persons conflict [3,4]. There have been various definitions of aggression. It has been traditionally, for instance, defined as unconcealed behavior that has the goal of causing physical damage on another individual [2,3,5,6]. Currently, aggressive behavior is mostly taken to be the overt harming of one person by another [7]. It may include violence, hostile, severe irritability, or "episodic dyscontrol" and assaultative behavior [5,8,9].

Psychopharmacology is one of field of pharmacology that addresses "the use of medications to correct or alleviate common mental illnesses" [8,10]. It can be also defined as a "scientific discipline that utilizes drugs to increase our knowledge and understanding of

the workings of the mind” [10]. It emphasizes drug induced changes in thinking, mood, and behavior [11]. On the other hand, psychopharmaceuticals are “medicaments affecting the behavior and subjective state of man and are used therapeutically on account of these psychotropic effect” [12]. Although we do not exactly know when the term psychopharmacology was first used, it has a new effective solution [8,12]. The fundamental purpose of this stream is not only to help disease but also to improve human nature, modify the personality, or cure bad habits [13]. It is becoming a pin point to people to depend on who have probably ignored their psychological problems because of money or time [8].

The key objective of research on aggression from a biomedical perspective is to develop novel therapies that can prevent, control or lessen harmful aggressive behavior among individuals [3,14]. When there is acceptable evidence that shows there are no scientific explanations for this behavior, however, an assessment and evaluation of psychotic symptoms have to be conducted [15]. In spite of the recognized limitations, the uses of animal models have great value in both pre-clinical analysis and clinical validation of psychotropic agents of human mental disorders [16].

There is recognizable advances and pharmacological progress in finding a medication to manage and treat pathological aggression although these therapeutic alternatives are still considered as far from satisfactory [1,3,17]. In spite of the unsatisfactory research on etiological studies, scientists are investigating more about pharmacologic interventions and their behavioral effects [8]. Thus, two approaches are emerging: one studying and identifying the main causes of the dysfunctions while the other investigating the alleviation of the behavior by pharmacological agents [18]. In all these processes, the development of a rational and evidence-based approach has to be warranted since there are potential risks with psychopharmacological intervention in the young population [19,20]. It has to be considered also that management of some types of aggression may require more than one treatment approach [21].

The different psychotropic agents used are designed to work in relation to the various mechanisms of the neurotransmitters [8]. Based on available information on the modes of actions and behavioural activity profiles of diverse other psychotherapeutic, it is often concluded that close interactions of different neurotransmitter systems ultimately dictate their ultimate [17].

Serotonergic Medications

Using various research modalities, serotonin (5-HT) is the CNS amine most studied in the context of aggressive behavior [8,19]. It is portrayed as a “civilizing” neurochemical and related excessive aggression and violence to deficiencies in serotonin levels [8]. The rationale to treat impulsive-aggressive patients with 5-HT-enhancing agents is related with the consistent findings of an inverse relationship between 5-HT and impulsive aggression [18].

Numerous open and blinded, placebo-controlled, studies have demonstrated the efficacy of these serotonergic medications, particularly with respect to the SSRIs (selective serotonin re-uptake inhibitors), which are drugs of choice in the treatment of depression [8,18]. Since 1990s various studies have very interestingly shown that pharmacological agents that activate or antagonize 5-HT_{1A}/IB and 5-HT_{2A}/C receptor subtypes, respectively, effectively suppress aggressive behavior in numerous animal models ranging from rodents, fish, guinea pigs to primates, invertebrates [22]. Antagonism of 5-HT₂ receptors tends to decrease aggression in animal models. This effect may explain the ability of newer antipsychotic agents (which, unlike the older medications, block 5-HT₂ receptors) to produce a reduction in aggression independent of their effects on psychotic symptoms [18].

5-HT Receptor Agonists

Direct-acting 5-HT receptor agonists have different chemical structures and diverse pharmacological properties, as it is possible to predict from the multiplicity of 5-HT receptor subtypes [23]. Pharmacological agents that act on 5-HT_{1A} and 5-HT_{1B} receptors may

provide a more effective alleviation in aggressive behavior than the current treatments with antipsychotic agents, selective serotonin reuptake inhibitors, and β -adrenergic blockers [24].

Non-Selective Serotonin Agonists

Etiological investigation has provided encouraging data in the non-selective serotonin agonists. These agonists, however, have shown particular selectivity in anti-aggressive effects. Specifically, significant research on eltoprazine has indicated that the drug provided the desired anti-aggressive effects while not inhibiting other behaviors, such as social interest and exploration [8].

Because of the double localization of both 5-HT_{1A} and 5-HT_{1B} receptors, systemically administered 5-HT_{1A} and 5-HT_{1B} receptor agonists in the antiaggressive dose-ranges have dual effects on serotonergic neurotransmission: by acting at the autoreceptors, they very effectively inhibit 5-HT neurotransmission. In contrast, when acting directly at postsynaptic sites, these agonists mimics the effect of 5-HT released, thereby mimicking enhanced 5-HT signaling. Thus, the net effect of a 5-HT_{1A} or 5-HT_{1B} receptor agonist on 5-HT_{1A} and 5-HT_{1B} signal transfer in postsynaptic areas represents a composite of decreased 5-HT release, resulting from autoreceptor activation, and a direct stimulation of the postsynaptic receptors [22].

Selective Serotonin Agonists

5-HT_{1A} Agonists

Selective 5-HT_{1A} receptor agonists have efficacious in suppressing aggressive behaviour, both on species—typical and in escalated aggression [8,24,25]. The role of these receptors in aggressive behavior was convincingly confirmed with selective 5-HT_{1A} receptor antagonist WAY-100,635, which effectively blocked the anti-aggressive effects of the agonists [24]. Several agonists show selectivity for the 5-HT receptor: 8-hydroxy-di-propylamino tetralin (8-OH-DPAT) is considered to be full agonist in experimental systems; anxiolytics such as buspirone ipsapirone, and gepirone and other ligands such as MDL 72832 are partial agonists. The only selective high-affinity silent antagonist at this receptor is WAY 100635 [23,26]. Additional ligands for this receptor include the agonists U-92016A and (+)-UH 301, and the putative antagonists (-)-UH 301 and NAD 299 [26].

Agonists at 5-HT_{1A} receptor sites such as, 8-hydroxy-2-(di-propylamino) tetralin hydrobromide, alnespirone, and S-15535, showed promising effects in laboratory animals [6,11]. Selective 5-HT_{1A} receptor agonists have efficacious anti-aggressive activity even though their sedative and motor suppressive effects may contribute to their anti-aggressive effect [24,25]. Additionally, the 5-HT_{1A} agonists are not specific to aggression [8].

A series of published single-case and open trials demonstrated that buspirone, whose action increases the release of serotonin, has anti-impulsive and antiaggressive effects in a variety of psychiatric diagnoses [15,23,28]. It is generally well tolerated, with the most frequently reported adverse events being headache, nervousness, and dizziness. It may also have efficacy in the treatment of dementia [29].

5-HT_{1B/D} Agonists

5-HT_{1B/D} receptor-selective agonists, such as sumatriptan, have unique properties that makes them effective in the treatment of acute migraine attacks. This effect results from constriction of intracranial blood vessels [8]. Additionally, other potential therapeutic uses of these drugs are being investigated; such as for gastric motor effect, autism, bipolar disorder and anti-aggressive effects [26]. The role of these receptors in aggression was confirmed with GR-127935, a selective 5-HT_{1D/B} receptor antagonist. This drug effectively blocked the anti-aggressive effects of the agonists [24].

The development of more selective agents for the 5-HT_{1B} receptors is advantageous, but which sites of action is the relevant (pre- vs.

post-synaptic receptors) becomes a question [25]. Actually, it was shown that 5-HT_{1B} agonists CP-93,129, CP-94,253, zolmitriptan and anpirtoline reduce aggression, without affecting motor activity [24,25]. This effect seems to be even more robust when aggression is escalated in some individuals like after social instigation or alcohol consumption [25].

Zolmitriptan is specific in reducing the species typical aggressive behavior as well as reducing alcohol heightened aggression with equal efficacy. The effects were postulated to be due to the activation of post-synaptic 5-HT_{1B/D} receptors [8]. The pharmacological effects of the triptans (e.g zolmitriptan) tend to be limited to the 5-HT₁ family of receptors. Clinically effective doses of these drugs correlate well with their affinities for both 5-HT_{1B}/5-HT_{1D} receptors. They interact potently with 5-HT_{1B}/5-HT_{1D} receptors. They have low/no affinity for other 5-HT receptors subtypes and other types of receptors such as α 1 and α 2 adrenergic, dopaminergic, cholinergic, and GABA receptors [23].

Drugs acting as 5-HT_{1B} agonist selectively decrease aggressive behaviors in mice probably via postsynaptic 5-HT_{1B} receptors. Agonists for the rodent 5-HT_{1B} receptors (named r5-HT_{1B}, homologue to the h5-HT_{1B} of humans) have been known since the development of anti-aggressive drugs called 'serenics' [25]. Serenics display a highly specific antiaggressive profile. This effect is caused by the activation of postsynaptic 5-HT_{1B} receptors because ligands affecting other 5-HT receptors have quite different antiaggressive effect [18].

The serious adverse effect of 5-HT₁ agonists is associated with their cardiac events, predominantly in patients with risk factors for coronary artery disease. The adverse effects can be coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, and atrial and ventricular arrhythmias [23]. So, they must not to be taken daily and for an extended period of time [8]. It is also important to note that these agonists have contrasting effects on sexual behavior, and food intake [24].

Serotonin Reuptake Inhibitors

Other trials have demonstrated significant results with serotonin reuptake inhibitors (SRIs). Response to selective serotonin re-uptake inhibitors (SSRIs) like fluoxetine supports the implication of the serotonergic system in aggressive obsessions [27]. Actually, these classes of drugs have been effectively used in the treatment of depression by correcting neurochemicals imbalances. They are designed to affect peripheral and central serotonin concentration. As their name indicates their specific mechanism is related with their ability to alter synaptic concentration of 5-HT by blocking the reabsorption of neuronally released 5-HT and decreasing the consequent presynaptic reaccumulation [23,28]. This finally increases the activity of the neurochemicals at the post synaptic sites [28,30]. That is why when selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine are administered, they potentiate and prolong the action of 5-HT and effective for the treatment of aggression [14].

Fluvoxamine, the other SSRI, was studied for its anti-aggressive effect in rodents for both maternal aggression and territorial aggression, and it appeared to be more effective for the former than the latter. Their nonspecific behavioral effects, however, have made them less successful in the treatment of aggression [8].

The other SRI which was tested for its anti-aggressive action in mice is clomipramine. It is one of TCAs (tricyclic antidepressants) [8]. Like other TCAs, it inhibits the uptake of norepinephrine and serotonin, and it was expected that it would have anti-aggressive effect. On empirical bases, the dosing range of the antidepressants for aggression is similar to that for depression [15]. The rationale for the use of antidepressant medication for the treatment of aggressive behavior is the observation of serotonin and noradrenalin metabolites have been found to be reduced in CSF (cerebrospinal fluid) from agitated patients with acquired brain injury (ABI) [9].

Mood stabilizers

Mood stabilizers are one of the first drugs of choices to control affective instability, impulsivity, aggressive behavior in various disorders

such as schizophrenia, unipolar depression personality disorders, and mental handicaps [15,28,31]. Among the mood stabilizers that use to reduce aggressive behavior, lithium and anticonvulsants are the most common [15].

Lithium

Lithium has been mainly used for the treatment of mania and as prophylactic agent in bipolar affective psychosis [32]. Its effectiveness in preventing suicide was also demonstrated by a retrospective cohort study. This study was accommodated a population based sample of 20638 health plan members who were diagnosed with bipolar disorder [28]. Very early on, lithium was suggested for the treatment of aggression related behaviors [15,29,33]. It was the first drug from this group shown to be effective in controlling aggressive behavior, in placebo-controlled and double-blind trial, in children who are with conduct disorder (CD) in the 1980s [12,15,34].

In his famous 1949 paper, John Cade was the first to propose that lithium might reduce aggression. Then several studies, the majority of them are open trials, were concentrated on the anti-aggressive and anti-impulsive effect of lithium on different diagnoses although its specific mechanism of action has not been distinguished yet [28]. Additional recent findings also demonstrated that certain agents from anticonvulsants and mood stabilizers, such as lithium and valproate (but not carbamazepine) may have neuroprotective properties. Specifically, valproate tends to attenuates apoptosis by enhancing the processing and transcription of Bcl-2the (B-cell lymphoma/leukemia-2 gene) [29].

Anticonvulsants

There has been interest in the behavioral effects of anti-seizure medications because of the aggressive behavior associated with epilepsy [6]. Anticonvulsants are being prescribed for behavioral problems with increasing frequency [29]. Anticonvulsant agents, such as carbamazepine and valproic acid, can be used to control chronic aggressive behavior [15].

Carbamazepine

Carbamazepine is an antiepileptic agent with psychotropic properties that are similar to lithium but with less neurotoxicity [29]. It has been shown to reduce aggressive behavior that may be related to epilepsy [8]. Importantly, a significant number of literatures are showing the efficacy of carbamazepine in the treatment of impulsive and aggressive behavior in different neurological disorders ranging from seizure disorder, middle cerebral arterial stroke, traumatic brain injury, attention deficit hyperactivity disorder, personality disorder, to Alzheimer's disease and schizophrenia [28]. As demonstrated by a double-blind placebo controlled study, carbamazepine with mean serum level of 5.3 µg/ml was effective in the treatment of aggression in a group of patients with mixed dementia and Alzheimer's disease [28,29]. It is not, however, recommended to control aggressive behavior because of the need to carefully monitor blood counts and liver function [8].

Valproate and Topiramate

The use of valproate (valproic acid and divalproex) followed the path of carbamazepine in psychiatry [28]. It is mainly anticonvulsant and also a mood stabilizer that is primarily used in the treatment of seizure disorders, mania, bipolar disorder, and migraine headaches [28,30]. It was later suggested in the treatment of aggressive behavior although the evidence is less persuasive in this condition [28]. Its main proposed mechanism of action is its effect on the function of the neurotransmitter GABA (Gama-AminoButyricAcid) [29,30].

Both valproate and topiramate are able to reduce aggressive behavior either as a single agent or in combination even though the former was more effective than the latter in reducing the intensity of agitation [28]. Topiramate was shown to be efficient in the suppression of impulsive aggressive behavior in patients with borderline personality disorder since it has effect on the avoiding of traumatic memories

that instigate the overreaction to the environmental alarms linked to the idea of abandonment and rejection [28]. Additionally, valproate, lamotrigine and levetiracetam have also been studied as a potential agent to control aggression in children with autism [30].

Antipsychotics

Antipsychotic, which are synonymous with major tranquilizers or neuroleptics, are calming medicaments used to decrease psychomotor stimulation and agitation, psychotic illusions, psychotic delusion, marked inner unrest, aggressive behavior, and severe insomnia [9,12]. They also have great value in studying the pathophysiology of schizophrenia and other psychoses [13]. Although the only well-established long-term indication is in the management of schizophrenia, they can be used in the short-term management of aggressive behavior [9,23]. Actually, the use of antipsychotic drugs led to dramatic changes in disease management decreasing life-long hospitalizations [13].

Drugs in this class are classified as either typical (also referred to as first generation) or atypical (second generation) antipsychotics [3,18,23]. This nomenclature originates from the high efficacy and lack of extrapyramidal side effects (EPSE) that were observed with atypical antipsychotics [23,31,34].

Typical neuroleptics

They are also named as traditional antipsychotic agents [31], first-generation neuroleptics [3,23,35] and conventional antipsychotics [9,34,35]. The summaries of product characteristics for drugs marketed in the years between 1997 and 2007 showed that these typicals have been used with broader clinical indications and wider dosage ranges [35]. The use of these medications in the management of aggressive behavior has largely been targeted at either reducing the psychotic thinking that may instigate aggressive behavior or sedating psychotic patients [18]. Conventionally the typicals, either the high-potency haloperidol or low-potency thioridazine/chlorpromazine, have been indicated to manage most psychopathology that is related with dementia [29]. Chlorpromazine and haloperidol are used as standards for evaluating new compounds against aggressive behavior because of their effectiveness [3].

The main drawbacks of these first-generation neuroleptics are their adverse effects such as parkinsonian symptoms (which is common in high-potency agents), peripheral anticholinergic effects (common in low-potency agents), postural hypotension, sedation, confusion, delirium, tardive dyskinesia, and akathisia [9,12,29]. In addition to these negative effects, they can produce acute dystonic reactions that might be a problem to identify in patients with communication problems [15]. Patients with brain injury may develop neuroleptic malignant syndrome [9]. As usual these agents should be carefully considered in elderly individuals before administration due to an increased number of falls or fractures associated with postural hypotension [29].

Atypical neuroleptics

Currently the pharmacotherapy of aggression mostly involves 'atypical' antipsychotics or the so called 'second generation' antipsychotics [3]. Some of these agents to be discussed here are clozapine, olanzapine, risperidone and quetiapine. Pharmacotherapy of aggressive behavior with typical neuroleptics may prove to be less effective than these newer antipsychotic agents [18]. Some limited evidences show that some of these 'second generation' agents may provide relief from disruptive behavior disorders related aggressive symptoms [33]. Importantly, the treatment options are showing that new 2nd or 3rd generation antipsychotics as well as some anticonvulsants are becoming the drugs of choice for treating chronic aggressive behavior [5].

In general, the second generations are safer and better tolerated than the typical neuroleptics [29,31,34]. This is because of their lower tendency than the latter one to cause EPSE (extra-pyramidal side effects) and tardive dyskinesia [31,34]. These agents can also have a sedative effect that might reduce impulsive aggressive behavior [3,28] although they are not preferable in chronic therapy because of their cognitive and motor consequences that interfere with day to day activities [3,28].

Clozapine is the prototype of atypical antipsychotics and it has low potency [13,36]. In spite of the absence of sufficient data for other psychiatric disorders, clozapine's effect against aggressive behavior was most commonly extracted in patients with schizophrenia [37]. The idea that clozapine is an effective pharmacological agent to treat aggressive behavior is followed and supported by clinical research, and it was more effective than haloperidol and risperidone [28].

The main disadvantage of clozapine is its severe anticholinergic effects and the need for routine blood count monitoring because of the increased risk of agranulocytosis [29,36]. This need for routine hematologic monitoring as well as increased risk for seizures made this drug usually not to be a first choice in purely autistic patients even though it can be considered for managing patients with treatment-resistant schizophrenia and autism-associated aggression [31]. In addition to that it is also effective in the treatment of aggressive behavior in patients with disorders other than schizophrenia [28].

Olanzapine can also be used in the treatment of aggressive behavior although the evidence does not give it the same status as clozapine [28]. In a small clinical case series, for instance, Soderstrom, *et al.* reported that olanzapine treatment of aggressive behavior caused rapid response in 5 out of 6 teenaged who were with neuropsychiatric [17]. It was effective in diminishing the target behavior, reducing aggression and self-injury, destructive and disruptive behaviors. It was also effective in treating aggression in patients with AD (Alzheimer's disease) and it may also reduce the frequency of aggressive incident in autistic individuals [15].

Risperidone is the most widely studied drug in aggression of children, and autism that display maladaptive aggressive behavior [3,18,31,34]. Consequently, it is usually used in child and adolescent psychiatry for different neuropsychiatric disorders [38]. It is one of the safest and efficacious medications for short-term and longer-term treatment of PA (pathological aggression) in children suffering from DBDs (Disruptive Behavior Disorders) [19]. Recently, some reports have suggested the efficacy of quetiapine in treating aggressive behavior in different psychiatric disorders and neurological diseases such as dementia, borderline personality disorder, conduct disorder in children, traumatic brain injury etc [28,29,34].

Conclusion

Much scientific investigation should be carried out to properly define the nature and level of aggression, and to characterize its pharmacotherapy as well as psychosocial treatment. Investigations to develop efficacious anti anti-aggressive drugs have to be our concern, particularly the serotonergic medications needs deep rooted analysis. Further research is mandatory to clarify the exact mechanism of actions of all neuropharmacological agents in relation to their use against aggression and to differentiate the safety and efficacy between typical and newer antipsychotics, the safety and efficacy of mood stabilizers in the treatment of aggression. Research on aggressive behavior has to be a 'hot topic' from different perspectives and various specialists from different profession has to be involved.

Conflict of Interest

No.

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