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Serotoninergic impairment and aggressive behavior in Alzheimer's disease

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Review

Abstract. The overall goal of all therapeutic interventions in Alzheimer's disease (AD) is to: (a) optimize the impaired functions and (b) restore an affordable quality of life for both the patient and his surroundings. AD has been characterized by a significant serotoninergic impairment. It is well known that impaired serotoninergic function is related to aggressive behavior. We, herein, review the past and recent evidence that seems to link the serotoninergic system with aggressive manifestations in AD patients. Managing the aggressive behavior of these patients might be of significant medical, social and economical importance. However, there is still a long way to go until we verify the exact pathophysiological mechanism(s) involved in the induction of aggression in AD patients. The current data underlines a complex relationship between the observed serotoninergic impairment in AD patients and the (a) cholinergic system, (b) the endocrine (hormonal) state, (c) the nutritional habits, (d) the genetic background and (e) the caregiving environment.

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INTRODUCTION

Alzheimer's disease (AD), that was originally described almost a century ago (Alzheimer 1907), is now considered as a very common brain disorder for the elderly and has become a disease of major health concern worldwide. In most patients who develop dementia, the core syndrome of cognitive dysfunction is superimposed over the course of the disease by behavioral disorders such as depression, anxiety, agitation, restlessness, aggression, disturbances of the sleep-wake cycle, delusions and hallucinations (Hock et al. 2000). Over the last decade, a series of genetic studies has significantly improved our knowledge over the pathogenesis of AD. The great diversity of clinical presentations in AD suggests that certain individual factors could possibly influence the disease phenotype. In addition to amyloid plaques and neurofibrillary tangles, the loss of neurons from certain transmitter source nuclei and the associated neurochemical alterations represent a pathologic hallmark of AD (Lai et al. 2003). Since neurotransmitters are the most important regulators of mood and perception, it seems quite reasonable that most (if not all) of the above mentioned neuropsychiatric symptoms might be related to selective degeneration of certain neurotransmitter systems (Forstl et al. 1994, Lam et al. 2004, Mintzer 2001).

The degeneration of cholinergic neurons (mainly in the hippocampus and the cortex) with a substantial decrease in acetylcholine (ACh) and choline acetyltransferase (ChAT) levels, was one of the earliest findings in AD (Karageorgiou 1999). Since the cholinergic system appears to play an important role in memory functions, the decreased ACh levels (found in AD brains) are though to be a main contributor to the observed cognitive disturbances (Francis et al. 1999). Cholinergic deficits seem to be a major contributory factor of neural susceptibility to additional neurochemical deficits and therefore, a considerable aspect of almost all AD clinical manifestations (Hope et al. 1997, Terry and Buccafusco 2003). There seems to be a link between the cholinergic system and other neural circuits (such as the serotoninergic) deficits, as found in *post mortem* AD brains (Garcia-Alloza et al. 2005).

Serotonin (5-HT; 5-hydroxytryptamine) has been linked to certain neuropsychiatric symptoms in AD, such as agitation, aggression, depression and psychosis (Lanctot et al. 2001). Treating these noncognitive

Table I

The main 5-HT receptor subtypes in humans

Receptor	Location	Main Effect
1A	CNS	Neuronal inhibition, sleep, feeding, thermoregulation, anxiety
1B	CNS, VSM	Presynaptic inhibition, behavioral effects, pulmonary vasoconstriction
1D	CNS, BV	Cerebral vasoconstriction, locomotion
2A	CNS, PNS, SM, PL	Neuronal excitation, behavioral effects, smooth muscle contraction, platelet aggregation etc.
2B	GF	Contraction
2C	CNS, CP	CSF secretion
3	CNS, PNS	Neuronal excitation, emesis, anxiety
4	CNS, PNS, GIT	Neuronal excitation, GI motility
5	CNS	Not known
6	CNS	Not known
7	CNS, GIT, BV	Not known

(CNS) central nervous system; (VSM) vascular smooth muscle; (BV) blood vessels; (PNS) peripheral nervous system; (SM) smooth muscle; (PL) platelets; (GF) gastric fundus; (CP) choroid plexus; (CSF) cerebrospinal fluid; (GIT) gastrointestinal tract; (GI) gastrointestinal. With a total of 14 subtypes, 5-HT receptors hold the record for diversity (for further details see Hoyer et al. 1994).

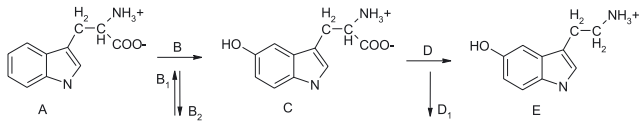

Fig.1. Synthesis of serotonin. (A) L-tryptophan (Trp); (B) tryptophan-5-monooxygenase; (B_1) O_2 + tetrahydrobiopterine; (B_2) H_2O + dihydrobiopterin; (C) L-5-hydroxytryptophan (5-HTP); (D) aromatic L-amino acid decarboxylase; (D_1) CO_2; (E): serotonin (5-HT).

symptoms is of significant importance for clinical practice, since they seem to be a major source of distress for both the demented elder and the patient's caregiver (Donaldson et al. 1997). Among these symptoms, aggression is well related to serotoninergic function in AD patients (Lanctot et al. 2002a, Mintzer 2001, Mintzer et al. 1998, Palmer et al. 1988, Procter et al. 1992). We, herein, review the past and recent evidence that seems to link the serotoninergic system with aggressive manifestations in AD patients.

SEROTONINERGIC IMPAIRMENT IN AD

It is known that 5-HT is present in the diet, but can also arise by biosynthesis via a pathway where the precursor amino acid is tryptophan (Trp). Trp is converted to 5-hydroxytryptophan (catalysed by tryptophane hydroxylase), which is then decarboxylated to 5-HT (by l-amino-acid decarboxylase) (Fig. 1). The mechanisms of synthesis, storage, release and reuptake of 5-HT are very similar to those of noradrenaline. The degradation pathway of 5-HT (Fig. 2) occurs, mainly, through oxidative deamination (by a monoamine oxidase, MAO) followed by oxidation to 5-hydroxyindoleacetic acid (5-HIAA). 5-HIAA is excreted in the urine and serves as an indicator of 5-HT body production/concentration. The actions of 5-HT are numerous and complex, accompanied by a considerable species variation and a significant receptor diversity (as shown on Table I).

The correlation between serotoninergic impairment and AD is well documented and manifested *via* a series of non-clinical and clinical features, such as: (a) alterations in 5-HT and 5-HIAA levels of the brain and the cerebrospinal fluid (CSF), (b) loss of 5-HT synthesizing neurons, (c) loss of 5-HT receptors, (d) numerable 5-HT receptor polymorphisms, and (e) response to several treatment schemes directed towards the improvement of serotoninergic function. However, it should be noted that the expression of these features is dependable on the genetic individuality, the followed (antipsychotic or other) treatment, the current stage of the disease, the accompanied pathology, and even the caregiving environment of the AD patient.

Alterations in 5-HT and 5-HIAA levels

Brain 5-HT concentrations were found decreased in *post mortem* studies of demented AD patients, compared to an age-matched healthy control group (Adolfsson et al. 1979). A joint study that was conducted in *post mortem* brain regions of cases without known brain pathology, showed an age-related decrease of 5-HT levels in the gyrus cinguli and an increase of 5-HT levels in the medulla oblongata (Carlsson et al. 1980). In senile dementia of the non-vascular type, 5-HT concentrations in brain region (such as the caudate nucleus and the hippocampus) samples were also found decreased (see Table II), suggesting that the process of neuronal aging might be accelerated in this type of dementia. In a study where 5-HT metabolism was assessed by measuring the concentration of 5-HIAA in *post mortem* brains from three groups (normal control subjects, AD and

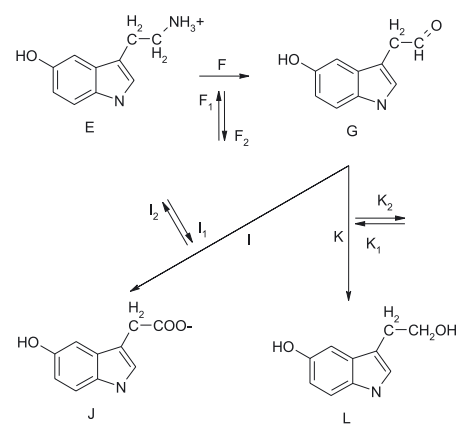

Fig. 2. Degradation of serotonin. (E) serotonin (5-HT); (F) monoamine oxidase (MAO); (F_1) H_2O + O_2; (F_2) NH_4^+ + H_2O_2; (G) 5-hydroxyindoleacetaldehyde; (I) aldehyde dehydrogenase; (I_1) H_2O + NAD^+; (I_2) H^+ + NADH; (J) 5-hydroxyindole acetic acid (5-HIAA); (K) aldehyde reductase; (K_1) H^+ + NADPH; (K_2) $NADP^+$; (L) 5-hydroxytryptophol.

Table II

Alterations in 5-HT and 5-HIAA levels of *post mortem* brain regions

Brain region	Observation	References
Amygdala	(-) 5-HT levels	Yates et al. (1986)
Caudate nucleus	(-) 5-HT levels	Carlsson et al. (1980), Gottfries et al. (1983), Yates et al. (1986)
Cortex	(-) 5-HIAA levels	Cross et al. (1983), Reinikainen et al. (1988)
Gyrus cinguli	(-) 5-HT levels	Arai et al. (1984), Carlsson et al. (1980), Gottfries et al. (1983)
Hippocampal cortex	(-) 5-HT levels	Reinikainen et al. (1988)
Hippocampus	(-) 5-HT levels	Carlsson et al. (1980), Gottfries et al. (1983), Reinikainen et al. (1988)
->>-	(-) 5-HIAA levels	Cross et al. (1983)
Hypothalamus	(-) 5-HT levels	Carlsson et al. (1980)
Medulla oblongata	(+) 5-HT levels	Carlsson et al. (1980)
Putamen	(-) 5-HIAA levels	Reinikainen et al. (1988)
Superior frontal gyrus	(-) 5-HT levels	Arai et al. (1984)
Thalamus	(-) 5-HIAA levels	Reinikainen et al. (1988)

(+) increased; (-) decreased. It should be noted, however, that the experimental data derived from post mortem material might lead to overestimation of the neurotransmitter deficit due to rapid 5-HT metabolism in non-fixed tissue. Thus, in each of the above studies, there seems to be certain dependence on the tissue-preparation conditions, on the method followed, as well as on the sensitivity of the latter.

depressed patients), 5-HIAA levels were significantly reduced in the hippocampus and certain cortical regions of the demented patients, but could not be correlated with the degree of any clinical AD manifestation (Cross et al. 1983). One year later, Arai and coauthors (1984) showed that AD brain samples had lower 5-HT mean concentrations in all regions (significant in 9 areas), while 5-HIAA levels were found reduced in 20 regions (significantly so in 8 areas). The maximal 5-HT concentration reductions were noted in the superior frontal gyrus and the cingulum (Table II).

CSF studies carried out 35 years ago reported a decrease of 5-HIAA and homovanillic acid (HVA) levels in senile and pre-senile patients, accompanied by a negative correlation between the two acids and the degree of the dementia (as represented by intellectual and emotional deterioration as well as social reduction) (Gottfries et al. 1969, 1970): the higher the degree of mental disturbances, the lower the concentrations of 5-HIAA and HVA. Renewal rates of cerebral 5-HIAA and HVA were also found reduced in AD patients (Guard et al. 1976), while 5-HT metabolism was found decreased *via* a CSF investigation on 10 patients with pre-senile Alzheimer's disease (Argentiero and Tavolato 1980). These findings were confirmed by Soininen and coauthors (1981), who also stated that 5-HIAA levels are reduced accordingly to the severity of the dementia. The outline of these studies was that the observed decrease in the levels of 5-HIAA may reflect an inhibited turnover of 5-HT (Whitford 1986).

Loss of 5-HT synthesizing neurons

The above data suggests that the serotoninergic system is widely affected in AD. However, a decrease in 5-HT synthesis might be secondary to degeneration and/or a loss of serotoninergic neurons (Whitford 1986). In AD, there are extensive losses of 5-HT synthesizing neurons in the dorsal and the median raphe nuclei, which provide the serotoninergic innervation to the forebrain (Aletrino et al. 1992, Halliday et al. 1992, Yamamoto and Hirano 1985). Moreover, studies have indicated a significant reduction of 5-HT re-uptake sites in the cortex (Chen et al. 1996, D'Amato et al. 1987). A disturbance of 5-HT turnover in AD patients was, earlier, also reported by Gottfries and Roos (1973). Benton and coauthors (1982) have studied the monoamine nerve terminals (using markers of both 5-

HT and catecholamine terminals) in temporal neocortex (acquired from 9 histologically confirmed AD cases), and found them to be significantly decreased in number compared to those of similar age controls. These findings were later confirmed by Bowen and coauthors (1983) through the use of non-enzymatic biological markers of the 5-HT synapse.

Moreover, the 5-HT nerve cells of AD necropsy samples demonstrated a significant nucleolar volume and cytoplasmic RNA content reduction by 31% and 38% respectively, in both the medial and the lateral divisions of the dorsal tegmental nucleus (Mann and Yates 1983). One year later, Cross and coauthors (1984) were the first to undertake an extensive ligand binding study (using 3H-LSD ligands) and to report significantly reduced 5-HT receptor binding levels ranging from -53% in the hippocampus to -26% in the frontal cortex. This study was of major importance, since it was the first to report that reduced ligand binding to cortical and hippocampal 5-HT receptors was an exclusive to the senile dementia of Alzheimer type (SDAT) feature.

Loss of 5-HT receptors

A highly significant decrease in 5-HT receptor density (42%) was also confirmed in *post mortem* brain tissues from patients clinically diagnosed as suffering from dementia (Reynolds et al. 1984). It is accepted that postsynaptic 5-HT(2A) receptors are found reduced in AD (Cross et al. 1986, Reynolds et al. 1984). However, the situation regarding 5-HT(1A) receptor density is not so clear. Some studies suggest that a significant reduction of these receptors exists in AD (Lai et al. 2003, Middlemiss et al. 1986), while others support a loss in receptor density that is lower than that of the 5-HT(2A) receptors mentioned above (Cross et al. 1988). These variations could be due to the diversity observed in the assay techniques and patient selection procedures followed in these studies. Garcia-Alloza and coauthors (2004) report a significant decrease of 5-HT(1B/1D) and 5-HT(6) receptor density in *post mortem* frontal and temporal cortex of AD patients, who have been assessed so by using the Mini-Mental State Examination (MMSE) and the Present Behavioral Examination (PBE). Moreover, 5-HT(1B/1D) receptor density in the frontal cortex was correlated to MMSE decline, supporting its implication in memory impairment.

Alterations in 5-HT receptor functionality

Recent studies have shown a significant association between several polymorphisms of the serotonin neurotransmission genes and AD neuropsychiatric symptoms. A 102T/C polymorphism of the 5-HT(2A) receptor gene is associated with a variety of psychiatric symptoms such as auditory hallucinations (Holmes et al. 1998), psychosis (Assal et al. 2004, Nacmias et al. 2001), abnormal impulse control disorder and seasonal affective pattern (Arias et al. 2001, Bjork et al. 2002, Correa et al. 2002, Gursoy et al. 2001) in AD patients.

The Cys23Ser polymorphism in the 5-HT(2C) receptor gene has been linked to visual hallucinations and hyperphagia in AD patients (Holmes et al. 1998). 5-HT(6) 267 C allele has been suggested to be associated with higher scores in Hamilton Depression Rating Scale (Liu et al. 2001). Moreover, a 44-base pair insertion/deletion of the 5-HT transporter (5-HTT) promoter region (5-HTTPR) was discovered (Heils et al. 1996). The 5-HTTPR alleles are defined by differing numbers of a 44-base pair GC-rich repetitive sequence. The basal transcriptional activity of the long variant (*L) is about 2.5- to 3-fold higher than that of the short variant (*S) (Collier et al. 1996, Heils et al. 1996). This differential rate of transcription results in a reduction of 5-HT reuptake sites by approximately 40% in *S/*S homozygotes and a reduction of approximately 30% for heterozygotes (*S/*L), suggesting that the *S allele is functionally dominant (Lesch et al. 1996). The 5-HTTPR*L allele and the *L/*L genotype were reported to be associated with psychosis and aggression (Sukonick et al. 2001, Sweet et al. 2001).

A variable number tandem repeat (VNTR) polymorphism in intron 2 of the 5-HTT gene was also associated with susceptibility to unipolar or bipolar depression (Ogilvie et al. 1996). However, it should be noted that this association was not confirmed in AD patients with depression (Li et al. 1997).

Treating the impaired serotoninergic function

A pilot study conducted by Lehmann and coauthors (1981) showed that tryptophan administration accompanied by increased tryptophan absorption was a necessary condition for mental state improvement of the elderly. However, this was not entirely confirmed by Smith and coauthors (1984). The administration of alaproclate (a specific 5-HT reuptake inhibitor) in

demented patients increased their capacity to cope with life, while irritability, aggression and intolerance were reduced (Bergman et al. 1983). Shaw and coauthors (1984) reported significantly lower tryptophan concentrations in the plasma of demented patients compared to those of age-matched controls. These findings could be due to lower tryptophan absorption (Lehmann 1979) which seems to be more common in demented patients (Lehmann et al. 1981).

CORRELATING AGGRESSION WITH SEROTONINERGIC IMPAIRMENT IN AD

Aggression is considered as a behavior with verbal or physical threats which, if carried out, would cause harm to others, self or property. It can be expressed as situational (provoked), non-situational (unprovoked), passive, physical or interictal. However, aggression is not a diagnosis by itself, but being potentially drug-induced (through either intoxication or withdrawal), it can be considered as a symptom of many conditions (including dementia, personality disorders, post-traumatic stress disorders, pre-menstrual syndrome, trauma or as an expression of emotional and behavioral motivations) (Hughes 1999).

For more than 30 years, biological psychiatrists have been exploring the possible relationship between serotoninergic impairment and human aggression (see reviews by Asberg et al. 1986, Bowen et al. 1992, Brown and Linnoila 1990, Coccaro 1992, Karageorgiou 1999, Kunik et al. 1994, Mintzer 2001). AD patients were soon defined as an interesting substrate of clinical and *post mortem* investigation, since they exert aggressive behavior and are easily studied due to their institutionalization.

Shaw and coauthors (1967) were the first to conduct a relative study, proving the existence of a relation between 5-HT and depressive suicides (there is still a long-standing view among many psychiatrists that suicide and violence towards others represent different manifestations of the same underlying aggressive tendency).

Among the large data acquired by the studies that followed, it might be worth mentioning that Asberg and coauthors (1984) reported that depressed patients with low CSF 5-HIAA levels are significantly more aggressive and anxious (based on Rorschach ratings) than patients with normal 5-HIAA levels, but equal ratings of depression. Brown and coauthors (1982) reported a significant association between aggressive behavior, suicide attempts and lower 5-HIAA levels, suggesting that altered 5-HT metabolism may significantly contribute to these behaviors, irrespectively of the diagnostic group in which they occur.

An interesting study, conducted by Lanctot and coauthors (2002b) on AD patients, showed that NPI (Neuropsychiatric Inventory) aggression scores were positively correlated to prolactin (PRL) concentrations following a d,l-fenfluramine challenge. In addition, aggressive patients showed a greater mean PRL increase than non-aggressive subjects, depending on the level of cognitive impairment and gender; suggesting a complex link between aggression and central serotoninergic dysfunction in AD.

Moreover, results from recent *in vivo* imaging (Parsey et al. 2002) and pharmacological challenge studies (Cleare and Bond 2000) indicate that reduced 5-HT(1A) receptor binding is related to aggressive traits in healthy subjects. Using *post mortem* tissues of well-characterized AD subjects, Lai and coauthors (2003) confirmed the above by demonstrating that 5-HT(1A) binding deficits are related to aggressive behaviors. Assal and coauthors (2004) concluded that the presence of 5-HT(2A) polymorphisms might act as a risk factor for the expression of psychosis and aggression in AD patients, while Garcia-Aloza and coauthors (2004) reported an association between aggression and the 5-HT(6) receptors/ChAT ratio of both the frontal and the temporal cortex of AD patients.

Lithium has been shown to reduce aggression and the frequency of episodes in learning disabilities (Langee 1990) and in patients with organic brain damage (Bellus et al. 1996), possibly *via* enhancement of the serotoninergic transmission. The administration of serotonin-selective reuptake inhibitors (SSRIs), such as citalopram and sertraline, could be beneficial for dementia and chronic aggression after head injury (Kim et al. 2001). Moreover, the use of anti-androgens is believed to be an effective treatment against the progression of AD psychopathology (Casadesus et al. 2004), since the serotoninergic impairment contributes to the regulation of hypothalamic and hypophyseal secretion and interferes with paracrine activity in both the digestive and the reproductive system (Zdrojewicz et al. 1998).

A more careful view of all the above data might determine: (a) the variety of the criteria used to determine the mental state of the demented patients taking part in clinical studies, (b) the absence of any violent type characterization (in many studies), (c) the variety of the aggression-estimating procedures followed for both living AD subjects and those mentioned in *post mortem* brain tissue studies, and (d) the absence of certain parameters (such as the caregiving state and the patient's nutritional habits) that might be of significant importance (for the expression of aggressive/depressive behavior and the severe serotoninergic impairment respectively). It is clear that more precise (and widely accepted) criteria are needed in order to maintain a coherent advance in the field.

CONCLUSIONS

The overall goal of all therapeutic interventions in AD is to (a) optimize the impaired functions and (b) restore an affordable quality of life for both the patient and his surroundings. Managing the aggressive behavior of AD patients might be of significant medical, social and economical importance. However, there is still a long way to go until we verify the exact pathophysiological mechanism(s) involved in the induction of aggression in AD patients, since the current data indicates a complex relationship between the serotoninergic impairment and the cholinergic system, the endocrine (hormonal) state, the nutritional habits, the genetic background and the caregiving environment. Pharmacological manipulation of the brain serotoninergic system might be beneficial in preventing or treating certain neuropsychiatric symptoms (such as aggression) in AD patients, but it is still not clear whether this can provide a safe and case-independent treating principle. The investigation of 5-HT receptor polymorphisms is, in this case, of crucial importance: if we establish a more definite association between the genetic individuality of the AD patient and the current antipsychotic drug therapy, a more effective and case-specific treating approach could be attempted.

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