

Altered Glutamate Neurotransmission and Behaviour in Dementia: Evidence from Studies of Memantine

P.T. Francis*

King's College London, Wolfson Centre for Age-Related Diseases, London, UK

Abstract: Behavioural symptoms are a significant problem in Alzheimer's disease (AD). Symptoms including agitation/aggression and psychosis reduce patient quality of life, significantly increase caregiver burden, and often trigger nursing home placement. Underlying changes in the serotonergic, noradrenergic and cholinergic systems have been linked to some behavioural problems, however, the use of antipsychotics in this population has been associated with significant safety concerns.

A role for the glutamate system in schizophrenia, as well as in anxiety and depression, has been suggested, and evidence is emerging for a role for dysfunctional glutamate neurotransmission (*via* *N*-methyl-D-aspartate (NMDA) receptors) in certain behavioural changes in dementia. For example, the NMDA receptor antagonist, memantine has been shown to improve cognition, function (activities of daily living, ADLs) and, more recently, agitation/aggression, and delusions in AD patients. To date, little information is available regarding the neurochemical basis of agitation/aggression. However, the frontal and cingulate cortices – specifically, the formation of neurofibrillary tangles in glutamatergic pyramidal neurones of these areas – are proposed as regional substrates of these behaviours.

Given that memantine displays a favourable tolerability profile, it is relevant to investigate the underlying mechanism linking memantine with the behavioural elements of AD. One hypothesis proposes that memantine corrects dysfunctional glutamatergic neurotransmission in the frontal and cingulate cortices, thereby normalising pathways responsible for causing agitation. An alternative hypothesis is based on the observation that increased tangle formation is associated with agitation, and on recent studies where memantine has been shown to reduce tau phosphorylation *via* glycogen synthase kinase (GSK)-3 or activation of protein phosphatase (PP)-2A, which might subsequently lead to reduced agitation.

Keywords: Alzheimer's disease, glutamate, neurofibrillary tangles, tau, agitation.

INTRODUCTION

Behavioural symptoms are observed at all stages of Alzheimer's disease (AD), and significantly impact AD management. Although the most severe behavioural difficulties are associated with more advanced disease, AD patients can present with depressive, agitated and aggressive behaviours at any stage – up to 70% of patients experience agitation and/or irritability within the first year of diagnosis [1, 2]. Symptoms such as agitation/aggression and psychosis have a negative impact on the quality of life and social interactions of patients and their families, and present a significant burden to carers in terms of distress and physical and mental exhaustion [3-6]. According to the recent Alzheimer Europe Dementia Carers' survey, behavioural symptoms are the most problematic area to cope with for 50% of carers (more so than cognition, reported as most problematic by 45% of carers), with agitation/aggression the most common cause of the problem (16%) [5]. Carer burden is associated with increased nursing home placement; as behavioural symptoms are considered a significant problematic area for carers, these symptoms may consequently be a frequent trigger for nursing home placement [5-8]. Furthermore, such behavioural symptoms are often socially inappropriate, can be attention-seeking or even abusive [9].

Existing treatments for behavioural symptoms in dementia are often only effective in the short-term and some carry an increased risk of significant cardiovascular problems and accelerated cognitive decline [10, 11]. Furthermore, recent warnings have been issued by the FDA for the use of atypical antipsychotics in dementia patients, due to an increased mortality risk [12]. Many of these drugs antagonise dopamine or serotonin receptor subtypes, although no specific mechanism has yet been identified. There is an evidence base for the safe use of antidepressants in dementia patients, but only for the treatment of depression [13]. In addition, acetylcholinesterase inhibitors seem to improve apathy and mood in AD, but not agitation/aggressive behaviour [14, 15]. It is clear that drugs with alternative mechanisms of action are required to treat trouble-

some behavioural symptoms, particularly agitation and aggressive behaviour, in patients with dementia. Of interest is new evidence from clinical studies of the *N*-methyl-D-aspartate (NMDA) receptor antagonist, memantine, which demonstrates improvement of these symptoms.

Memantine is indicated for the treatment of moderate to severe AD, and has been shown to improve behavioural, cognitive and functional (i.e., ADL-related) symptoms in this patient population [16-18]. Memantine is also well tolerated, with rates of serious adverse events and mortality that are comparable to those of placebo treatment [19]. Specific behavioural aspects of AD that are influenced by memantine treatment, as assessed using the Neuro-psychiatric Inventory (NPI), include delusions, agitation/aggression, and irritability/lability [20-26].

Two hypotheses for the mechanisms of action that underlie memantine's effect on behavioural symptoms are presented with the hope that such a review will stimulate further research in this important area.

GLUTAMATE AND BEHAVIOUR

Normal glutamatergic neurotransmission and the main processes and molecules involved are illustrated in Fig. (1a), and have been reviewed in detail elsewhere (Danbolt, 2001) [27].

Glutamate is the major excitatory neurotransmitter of the cortex and hippocampus and is involved in many aspects of higher mental function. In particular, loss and dysfunction of both the pre- and postsynaptic glutamatergic system have been linked to cognitive dysfunction in AD [28-30]. There is evidence for an involvement of glutamate neurotransmission in psychosis, leading to the development of the glutamate hypothesis of schizophrenia – this hypothesis originated from the psychotomimetic action of phencyclidine (PCP), a non-competitive NMDA receptor antagonist. It is currently postulated that abnormalities in dopamine and glutamate neurotransmission are interconnected in the pathophysiology of AD; NMDA hypofunction in the prefrontal cortex may generate dysregulation of the dopamine system that, in turn, affects the glutamate-mediated systems [31, 32]. There is also evidence supporting the involvement of glutamate neurotransmission in the cause and

*Address correspondence to this author at the King's College London, Wolfson Centre for Age-Related Diseases, London SE1 1UL, UK; Tel: +44 (2) 07 848 6269; Fax: +44 (0) 207 848 6240; E-mail: paul.francis@kcl.ac.uk

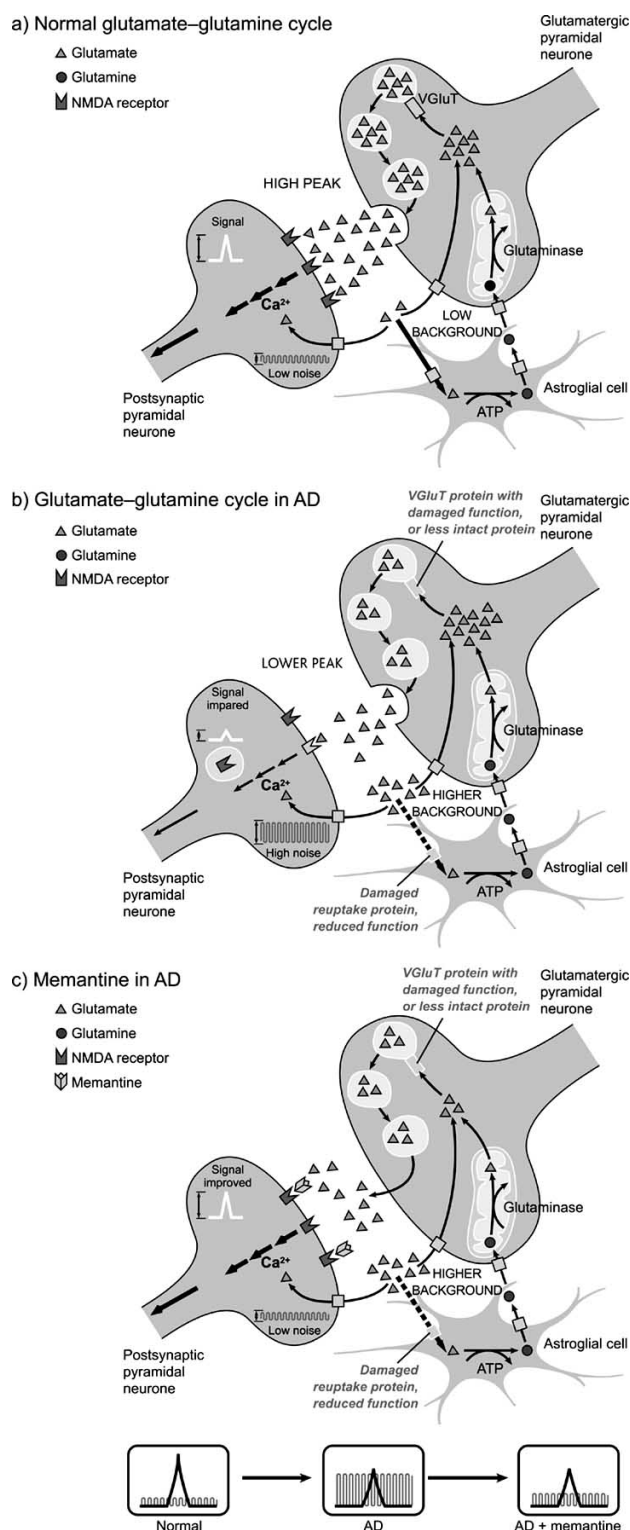


Fig. (1). Glutamatergic neurotransmission, its disruption in Alzheimer's disease, and a hypothesis for the effect of memantine (see text for explanation, and also Parsons *et al.* 1993; Parsons *et al.* 1999; Francis, 2005; Francis, 2006) [29, 36, 39, 45].

treatment response of depression [33]. Many studies link changes in the serotonergic system to aggressive behaviour, although the postsynaptic location of most serotonergic receptors, including those positioned on glutamatergic pyramidal neurones, suggests a role for glutamate neurotransmission [34]. Further evidence for this pro-

posal comes from neuropathological studies that demonstrated that neurofibrillary tangle (NFT) formation in the orbitofrontal cortex correlates with agitation/aggressive behaviour in AD patients [35]. When considered in conjunction with new clinical data indicating that memantine improves agitation/aggressive behaviour in AD patients, a role for the glutamatergic system in causing these symptoms is implicated.

Action of Memantine on the Glutamatergic System

Memantine is a moderate affinity, un-competitive, voltage-dependent NMDA receptor antagonist. In many ways, its action is similar to that of the endogenous NMDA antagonist Mg^{2+} , rather than other voltage-dependent antagonists such as PCP or use-dependent antagonists such as MK-801. The explanations for these differences centre on the faster blocking/unblocking kinetics and greater voltage dependency of memantine as compared with these molecules [36, 37].

In AD, it is proposed that dysfunctional glutamate neurotransmission produces an elevated baseline level of glutamate at the synapse, triggering inappropriate Ca^{2+} influx through the NMDA receptor, and impairing the usual detection of physiological signals (low signal-to-noise ratio) (see Fig. (1b)) [36, 38]. Preclinical studies have shown that, because of its specific level of voltage dependency, memantine can block the induction of signals likely to be caused by elevated baseline levels of glutamate, while still allowing physiological transmission [38, 39]. Therefore, in AD, memantine is proposed to improve the signal-to-noise ratio, by selectively reducing the noise level, and hence improves cognitive function (see Fig. (1c)) [36, 38]. In addition, *in vitro*, memantine has been shown to reduce the level of beta-amyloid ($A\beta$) protein – deposits are a defining feature of AD pathology, which have been shown to reduce glutamatergic transmission *via* the internalisation of NMDA receptors¹ [40].

Therefore, in the following section, I discuss a hypothesis for the action of memantine in improving agitation/aggressive behaviour *via* correction of glutamatergic neurotransmission. A second, contrasting hypothesis also considers the potential involvement of memantine in the reduction of NFT formation, through influence on the phosphorylation of tau.

HYPOTHESIS I: CORRECTION OF GLUTAMATERGIC NEUROTRANSMISSION IN A CORTICAL REGION RESPONSIBLE FOR AGITATION

Frontal lobe dysfunction and the presence of NFTs in the frontal and cingulate cortices, are associated with agitation/aggression in AD [35, 41]. It has been suggested that this pathology may reduce the threshold that triggers agitated behaviour, thereby generating an apparently exaggerated response to the effects of other symptoms, e.g., depression, and to environmental factors [41]. Therefore, in the first hypothesis, I consider whether memantine produces its behavioural effect in AD by correcting dysfunctional glutamatergic neurotransmission in the frontal and cingulate cortices.

Approximately 70% of cortical neurones use glutamate as a neurotransmitter and hence the glutamatergic system plays an important role in all regions of the cortex and hippocampus. Evidence for a pivotal role of glutamate in learning and memory is long-established [16, 28, 42], however, it is likely that any function of a particular cortical region will depend on glutamate neurotransmission at some level. One particular feature of the glutamatergic syn-

¹Lahiri, D. K.; Chen, D.; Alley, G. M.; Banerjee, P. K. Effects of memantine on the activity of secretase enzymes in the human neuroblastoma cells. Abstract presented at the 10th International Conference on Alzheimer's Disease and Related Disorders (ICAD), Madrid, Spain, 15-20 July 2006.

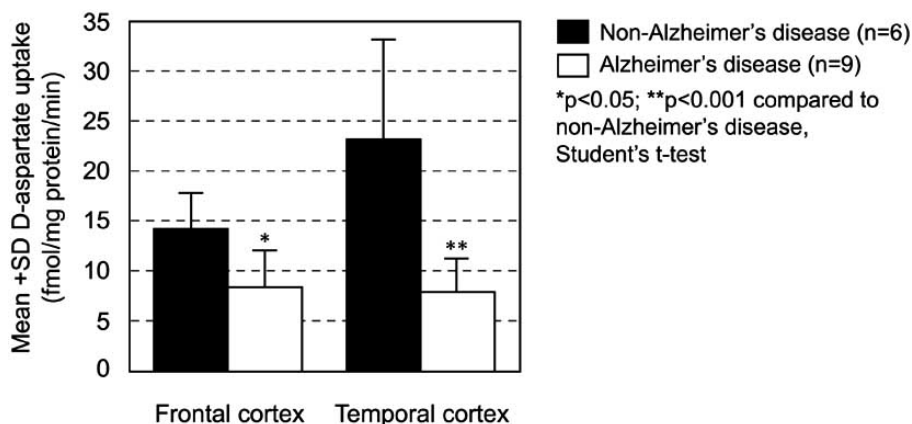


Fig. (2). Reduced glutamate reuptake, as measured using [^3H]D-aspartate, in the frontal and temporal cortices of patients with Alzheimer's disease [46].

apse is the NMDA receptor, which acts as a co-incident detector in long-term potentiation (LTP) formation [43, 44]. A vital part of this mechanism is the transient high peak of glutamate in the synaptic cleft during depolarisation, detected against a low resting background level (high signal-to-noise ratio) (see Fig. (1a)).

In AD, there is evidence that glutamate release and uptake are chronically decreased (see Fig. (1b)) [28, 45]; and that this interferes with neural activity in many cortical regions and the functions that they subserve. For example, reduced glial glutamate uptake is reported in AD (Fig. (2)) [46], reflecting oxidative damage to the transporters [47, 48]. Additionally, there is loss of the vesicular glutamate transporter (VGLUT) in several cortical regions (Fig. (3)) [30]. Such changes are likely to generate an elevated baseline level of glutamate at the synapse, triggering inappropriate Ca^{2+} influx. These raised background levels of glutamate impair the usual detection of physiological signals (low signal-to-noise ratio), disrupting normal cognitive processes [36]. Furthermore, the disruption of vesicular glutamate transport results in less glutamate being stored in pre-synaptic vesicles, reducing the level of signal upon neurotransmitter release [29, 30]. At extreme, abnormally high levels, synaptic glutamate and hence intracellular Ca^{2+} , can also cause neurotoxicity – a process that has been implicated in neurodegeneration in AD [49]. However, even mildly elevated background concentrations of glutamate are likely to have deleterious effects on signalling at these synapses, through an impaired signal-to-noise ratio at NMDA receptors.

In addition, deposits of $\text{A}\beta$ can reduce glutamatergic transmission by inducing the internalisation of NMDA receptors [40]. This pathological effect has been shown to disrupt NMDA-induced receptor currents, inhibiting long-term potentiation (LTP – synaptic plasticity) and signalling to downstream targets such as Akt (also known as protein kinase B) [40, 50, 51].

Therefore, *via* an influence on glutamatergic transmission, memantine could potentially impact upon AD pathology. Any subsequent evidence linking NMDA receptor dysfunction to specific symptomatic effects such as agitation/aggression, could help to explain the differential effects of memantine, as compared with therapeutic agents targeting other neurotransmitter systems. However, to date, there has been little study of this potential relationship between the glutamatergic system and agitation/aggression. Instead, the focus has been on the relationship between changes in the glutamatergic system, including NMDA receptors, and cognitive symptoms – particularly because of the link with LTP. As a consequence, AD pathology in relation to cognitive performance has been studied extensively.

It is of course possible that regions other than those linked here to agitation may be a substrate for the action of memantine on agitation. For example, the increase in irritability and agitation towards night time, the so-called 'sundowner' syndrome, may be associated with disruption of the entrainment of the light–dark cycle [52]. One may, therefore, speculate that glutamatergic transmission in the retinohypothalamic tract may be normalised by the action of me-

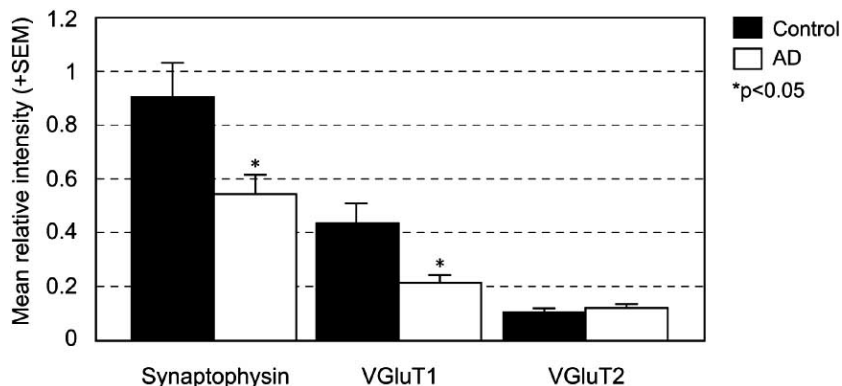


Fig. (3). Reduced synaptophysin and VGLuT1 in the parietal cortex of patients with Alzheimer's disease [30].

Reproduced with permission from Kirvell, S. L.; Esiri, M.; Francis, P. T. Down-regulation of vesicular glutamate transporters precedes cell loss and pathology in Alzheimer's disease. *J. Neurochem.* 2006, 98(3), 939-950. © 2006 Wiley-Blackwell Publishing Limited.

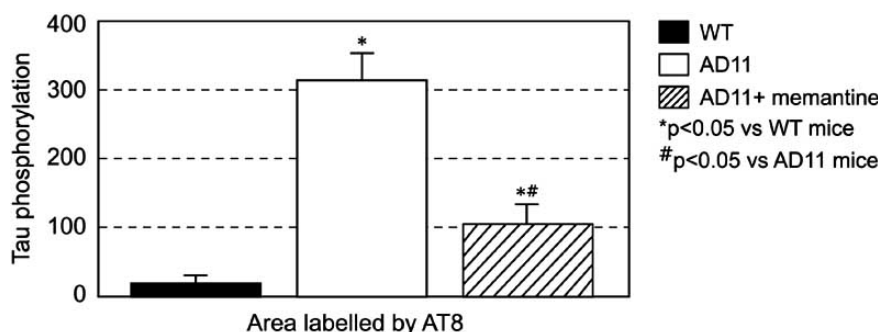


Fig. (4). Memantine reduces tau phosphorylation in AD11 mice (Egebjerg, J., *et al.* 2005).

Phosphorylated tau (AT8) was detected using tau epitope-directed antibodies. Memantine treatment rescues the percent area occupied by AT8-positive neurones in the entorhinal cortex. WT=wild type.

Reproduced with kind permission of Dr Jan Egebjerg² (2005).

memantine and the specific actions on agitation may flow from this mechanism [53].

HYPOTHESIS II: REDUCTION OF NEUROFIBRILLARY TANGLE (NFT) FORMATION, THROUGH INFLUENCE ON THE PHOSPHORYLATION OF TAU

Hyperphosphorylated tau is the primary component of NFTs, and NFT density in the frontal and cingulate cortices has been shown to correlate with the NPI item agitation/aggression in AD [35]. It is, however, worth noting that other conditions involving some type of agitation/aggression (e.g., schizophrenia) are not associated with NFT formation.

In the second hypothesis, therefore, I consider whether memantine improves agitation/aggression by reducing NFT formation in pyramidal neurones through actions on the phosphorylation state of tau.

Tau Phosphorylation in the AD Brain

Tau is a microtubule-associated phosphoprotein that, under normal conditions, mediates the assembly and maintenance of microtubules. However, if hyperphosphorylated, normal tau function is reduced, leading to the destabilisation of microtubules – with negative consequences for axonal transport, and probably neurodegeneration [54, 55]. These abnormally hyperphosphorylated forms of tau are the major protein subunit of NFTs [54, 56], and are characteristic features of the AD brain.

The regulation of tau phosphorylation has been linked to the actions of glycogen synthase kinase-3 (GSK-3) and protein phosphatase 2A (PP-2A). GSK-3 is the main candidate for the phosphorylation of tau, and has also been associated with a variety of other intracellular signalling-related actions, regulating neuronal plasticity, gene expression and cell survival, and also promoting the production and action of A β [55, 56]. GSK-3 is therefore closely associated with the prominent features of AD pathology.

PP-2A is also thought to be connected with the pathological effects of tau. PP-2A mediates the activity of tau *via* dephosphorylation, however, in AD, its activity is compromised [54]. Interestingly, activation of the NMDA receptor has also been linked with the reduction of PP-2A activity *in vitro* [57], and this is one factor that has prompted the study of memantine in relation to tau phosphorylation.

Memantine and Tau Phosphorylation

Although speculative at this stage, emerging evidence suggests that memantine may influence the status of tau phosphorylation, acting *via* either GSK-3 or PP-2A.

Memantine increases the pool of phosphorylated (i.e., inactive) GSK-3 by stimulating its serine phosphorylation [56]. A relatively high dose of memantine (50 mg/kg) administered to mice increased the phosphorylation of GSK-3 β at serine-9 in the cerebral cortex after 2 hours, with no change in total GSK-3 β [56]. Exact details of this mechanism of action are unknown, but there is some evidence from *in vivo* studies that the kinase, Akt, may be involved [56].

In vitro studies have shown that memantine is able to reverse the inhibition of PP-2A [54]. Treatment of organotypic cultures of rat hippocampal slices with 100 nM okadaic acid reduced PP-2A activity [54]. Treatment with memantine 10 μ M, but not 1 μ M, reversed this change [54]. The concentration required (10 μ M) is at the high end of what is considered to be therapeutically relevant. Memantine has also been shown to reduce the abnormal hyperphosphorylation of tau in AD11 transgenic mice². These transgenic mice express anti-nerve growth factor antibodies that neutralise the actions of NGF, and recapitulate many aspects of AD pathology including increased tau phosphorylation in the entorhinal cortex [58-60]. At 4.5 months of age, AD11 mice were treated for 90 days with 30 mg/kg/day memantine in the drinking water to reach a clinically relevant plasma level of approximately² 1 μ M. Parallel groups of wild type (WT) and AD11 mice with/without memantine treatment were sacrificed at 7.5 months of age and the percentage of phosphorylated forms of tau in brain areas was detected using AT8 and AT270 antibodies². Memantine treatment prevented the phenotypic increase in tau phosphorylation in the entorhinal cortex (see Fig. (4))². Recently, memantine has been shown to reduce brain levels of hyperphosphorylated tau in triple transgenic AD mice following three months of treatment³. There is further *in vitro* evidence that memantine inhibits the action of the protein, I₂^{PP2A} – itself an inhibitor of PP-2A [61]. The involvement of the NMDA receptor in mediating PP-2A activity (as described earlier) may also be implicated in the mechanism underlying the effect of memantine on PP-2A [57].

Clearly, further evidence, including investigation of the concentration/dose dependency of these tau-related effects, is required to support the initial findings. However, initial clinical support for these tau-related effects comes from a recent study in which memantine was shown to reduce levels of phosphorylated tau in the cerebrospinal fluid of AD patients, after 1 year of treatment [62]. A

²Egebjerg, J.; Westlind-Danielsson, A.; Capsoni, S.; Cattaneo, A. Memantine reverses *in vivo* tau hyperphosphorylation and a behavioural deficit in a mouse model of Alzheimer's Disease. Poster presented at the 7th International Conference on Alzheimer's and Parkinson's Diseases (AD/PD), Sorrento, Italy, 9-13 March 2005.

³Martinez-Coria, H.; Green, K. N.; Banerjee, P. K.; LaFerla, F. M. Memantine improves cognitive function and reduces brain levels of β -amyloid and hyperphosphorylated tau in a mouse model of Alzheimer's disease. *Soc. Neurosci.* 2007, Abstract 548.2.

further test of this mechanism of action would be the effect of other GSK-3 β inhibitors, such as lithium or those currently under development, on agitation. Indeed, there is some – however limited – evidence of the efficacy of lithium in the treatment of aggression [63].

SUMMARY

Behavioural symptoms are a troublesome aspect of AD, often becoming disruptive and/or aggressive as the disease progresses. However, there is some concern over the safety of existing antipsychotic medications used for the treatment of AD. The NMDA receptor antagonist, memantine, has demonstrated efficacy and safety in the treatment of behavioural symptoms in patients with moderate to severe AD, and specific benefit has been noted in the domain of agitation/aggression. Therefore, with relevance to the ongoing development of pharmacological treatments for AD, it is informative to investigate the link between the memantine mechanism of action and the underlying neuropathology of behavioural dysfunction in AD. Although no direct evidence for this connection is currently available, two hypotheses have been proposed suggesting a link *via* glutamate transmission and tau phosphorylation. To assist in making the association between neuropathology and the induction of agitation, and to aid in appropriate patient management, a clear definition of specific behavioural symptoms must be available for clinical analysis.

ACKNOWLEDGEMENT

The author wishes to acknowledge the editorial assistance of Juliet George and Jenny Muiry during the preparation of this manuscript.

CONFLICTS OF INTEREST

I have received honoraria for speakers bureau from companies involved in developing and marketing drugs for Alzheimer's disease (Lundbeck, Forest, Pfizer, Eisai and BTG).

REFERENCES

- Jost, B. C.; Grossberg, G. T. The evolution of psychiatric symptoms in Alzheimer's disease: a natural history study. *J. Am. Geriatr. Soc.* **1996**, *44*(9), 1078-1081.
- Lopez, O. L.; Becker, J. T.; Sweet, R. A.; Klunk, W.; Kaufer, D. I.; Saxton, J.; Habeych, M.; DeKosky, S. T. Psychiatric symptoms vary with the severity of dementia in probable Alzheimer's disease. *J. Neuropsychiatry Clin. Neurosci.* **2003**, *15*(3), 346-353.
- Potts, H. W.; Richie, M. F.; Kaas, M. J. Resistance to care. *J. Gerontol. Nurs.* **1996**, *22*(11), 11-16.
- Banerjee, S.; Smith, S. C.; Lamping, D. L.; Harwood, R. H.; Foley, B.; Smith, P.; Murray, J.; Prince, M.; Levin, E.; Mann, A.; Knapp, M. Quality of life in dementia: more than just cognition. An analysis of associations with quality of life in dementia. *J. Neurol. Neurosurg. Psychiatry* **2006**, *77*(2), 146-148.
- Georges, J.; Jansen, S.; Jackson, J.; Meyrieux, A.; Sadowska, A.; Selmes, M. Alzheimer's disease in real life – the dementia carer's survey. *Int. J. Geriatr. Psychiatry* **2008**, *23*(5), 546-551.
- Matsumoto, N.; Ikeda, M.; Fukuhara, R.; Shinagawa, S.; Ishikawa, T.; Mori, T.; Toyota, Y.; Matsumoto, T.; Adachi, H.; Hirono, N.; Tanabe, H. Caregiver burden associated with behavioral and psychological symptoms of dementia in elderly people in the local community. *Dement. Geriatr. Cogn. Disord.* **2007**, *23*(4), 219-224.
- Ferris, S. H.; Steinberg, G.; Shulman, E.; Kahn, R. N.; Reisberg, B. Institutionalization of Alzheimer's disease patients: reducing precipitating factors through family counseling. *Home Health Care Serv. Q.* **1987**, *8*, 23-51.
- Yaffe, K.; Fox, P.; Newcomer, R.; Sands, L.; Lindquist, K.; Dane, K.; Covinsky, K. E. Patient and caregiver characteristics and nursing home placement in patients with dementia. *JAMA* **2002**, *287*(16), 2090-2097.
- Cohen-Mansfield, J. Agitated behaviors in the elderly. II. Preliminary results in the cognitively deteriorated. *J. Am. Geriatr. Soc.* **1986**, *34*(10), 722-727.
- McShane, R.; Keene, J.; Gedling, K.; Fairburn, C.; Jacoby, R.; Hope, T. Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. *BMJ* **1997**, *314*, 266-270.
- Ballard, C.; Waite, J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst. Rev.* **2006**:CD003476.
- Schneider, L. S.; Dagerman, K. S.; Insel, P. Risk of death with atypical antipsychotic drug treatment for dementia. *JAMA* **2005**, *294*, 1934-1943.
- Sink, K. M.; Holden, K. F.; Yaffe, K. Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. *JAMA* **2005**, *293*(5), 596-608.
- Gauthier, S.; Feldman, H.; Hecker, J.; Vellas, B.; Ames, D.; Subbiah, P.; Whalen, E.; Emir, B.; Donepezil MSAD Study Investigators Group. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *Int. Psychogeriatr.* **2002**, *14*, 389-404.
- Howard, R. J.; Juszcak, E.; Ballard, C. G.; Bentham, P.; Brown, R. G.; Bullock, R.; Burns, A. S.; Holmes, C.; Jacoby, R.; Johnson, T.; Knapp, M.; Lindsay, J.; O'Brien, J. T.; Wilcock, G.; Katona, C.; Jones, R. W.; DeCesare, J.; Rodger, M.; CALM-AD Trial Group. Donepezil for the treatment of agitation in Alzheimer's disease. *N. Engl. J. Med.* **2007**, *357*(14), 1382-1392.
- Winblad, B.; Möbius, H. J.; Stöffler, A. Glutamate receptors as a target for Alzheimer's disease – are clinical results supporting the hope? *J. Neural. Transm.* **2002**, (Suppl) *62*, 217-225.
- Reisberg, B.; Doody, R.; Stöffler, A.; Schmitt, F.; Ferris, S.; Möbius, H. J.; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *New Engl. J. Med.* **2003**, *348*, 1333-1341.
- Tariot, P. N.; Farlow, M. R.; Grossberg, G. T.; Graham, S. M.; McDonald, S.; Gergel, I.; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil. A randomized controlled trial. *JAMA* **2004**, *291*(3), 317-324.
- European Medicines Evaluation Agency. *Ebixa EPAR, CHMP Variation Assessment Report*. Scientific Discussion. November **2005**.
- Cummings, J. L.; Mega, M.; Gray, K.; Rosenberg-Thompson, S.; Carusi, D. A.; Gornbein, J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **1994**, *44*, 2308-2314.
- Cummings, J. L. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. *Neurology* **1997**, *48*(5 Suppl 6), S10-S16.
- Gauthier, S.; Wirth, Y.; Möbius, H. J. Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *Int. J. Geriatr. Psychiatry* **2005**, *20*(5), 459-464.
- Gauthier, S.; Loft, H.; Cummings, J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *Int. J. Geriatr. Psychiatry* **2008**, *23*(5), 537-545.
- Cummings, J. L.; Schneider, E.; Tariot, P. N.; Graham, S. M. Behavioural effects of memantine in Alzheimer's disease patients receiving donepezil treatment. *Neurology* **2006**, *67*, 57-63.
- Wilcock, G. K.; Ballard, C. G.; Cooper, J. A.; Loft, H. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *J. Clin. Psychiatry* **2008**, *69*(3), 341-348.
- McShane, R.; Areosa Sastre, A.; Minakaran, N. Memantine for dementia. *Cochrane Database Syst. Rev.* **2006**, *2*, CD003154.
- Danbolt, N. C. Glutamate uptake. *Prog. Neurobiol.* **2001**, *65*(1), 1-105.
- Francis, P. T.; Sims, N. R.; Procter, A. W.; Bowen, D. M. Cortical pyramidal neurone loss may cause glutamatergic hypoactivity and cognitive impairment in Alzheimer's disease: investigative and therapeutic perspectives. *J. Neurochem.* **1993**, *60*(5), 1589-1604.
- Francis, P. T. The interplay of neurotransmitters in Alzheimer's disease. *CNS Spectr.* **2005**, *10*, 6-9.
- Kirvell, S. L.; Esiri, M.; Francis, P. T. Down-regulation of vesicular glutamate transporters precedes cell loss and pathology in Alzheimer's disease. *J. Neurochem.* **2006**, *98*(3), 939-950.
- Tamma, C. A. Schizophrenia and glutamatergic transmission. *Crit. Rev. Neurobiol.* **1998**, *12*(1-2), 21-36.
- Laruelle, M.; Frankle, W. G.; Narendran, R.; Kegeles, L. S.; Abi-Dargham, A. Mechanism of action of antipsychotic drugs: from dopamine D(2) receptor antagonism to glutamate NMDA facilitation. *Clin. Ther.* **2005**, *27*(Suppl A), S16-S24.
- Paul, I. A.; Skolnick, P. Glutamate and depression: clinical and preclinical studies. *Ann. N.Y. Acad. Sci.* **2003**, *1003*, 250-272.
- Olivier, B.; van Oorschot, R. 5-HT1B receptors and aggression: a review. *Eur. J. Pharmacol.* **2005**, *526*(1-3), 207-217.
- Tekin, S.; Mega, M. S.; Masterman, D. M.; Chow, T.; Garakian, J.; Vinters, H. V.; Cummings, J. L. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. *Ann. Neurol.* **2001**, *49*, 355-361.
- Parsons, C. G.; Danysz, W.; Quack, G. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist – a review of pre-clinical data. *Neuropharmacology* **1999**, *38*, 735-767.
- Parsons, C. G.; Stöffler, A.; Danysz, W. Memantine: a NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system – too little activation is bad, too much is even worse. *Neuropharmacology* **2007**, *53*(6), 699-723.
- Danysz, W.; Parsons, C. G.; Möbius, H. J.; Stöffler, A.; Quack, G. Neuroprotective and symptomatological action of memantine relevant for Alzheimer's disease – a unified glutamatergic hypothesis on the mechanism of action. *Neurotox. Res.* **2000**, *2*(2-3), 85-97.

- [39] Parsons, C. G.; Gruner, R.; Rozental, J.; Millar, J.; Lodge, D. Patch clamp studies on the kinetics and selectivity of N-methyl-D-aspartate receptor antagonism by memantine (1-amino-3,5-dimethyladamantan). *Neuropharmacology* **1993**, *32*(12), 1337-1350.
- [40] Snyder, E. M.; Nong, Y.; Almeida, C. G.; Paul, S.; Moran, T.; Choi, E. Y.; Nairn, A. C.; Salter, M. W.; Lombroso, P. J.; Gouras, G. K.; Greengard, P. Regulation of NMDA receptor trafficking by amyloid-beta. *Nat. Neurosci.* **2005**, *8*, 1051-1058.
- [41] Senanarong, V.; Cummings, J. L.; Fairbanks, L.; Mega, M.; Masterman, D. M.; O'Connor, S. M.; Strickland, T. L. Agitation in Alzheimer's disease is a manifestation of frontal lobe dysfunction. *Dement. Geriatr. Cogn. Disord.* **2004**, *17*, 14-20.
- [42] Danysz, W.; Zajackowski, W.; Parsons, C. G. Modulation of learning processes by ionotropic glutamate receptor ligands. *Behav. Pharmacol.* **1995**, *6*, 455-474.
- [43] Bliss, T. V.; Collingridge, G. L. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **1993**, *361*(6407), 31-39.
- [44] Lynch, G. Memory and the brain: unexpected chemistries and a new pharmacology. *Neurobiol. Learn. Mem.* **1998**, *70*(1-2), 82-100.
- [45] Francis, P. T. Glutamatergic systems in Alzheimer's disease. *Int. J. Geriatr. Psychiatry* **2003**, *18*(Suppl 1), S15-S21.
- [46] Procter, A. W.; Francis, P. T.; Holmes, C.; Webster, M.-T.; Qume, M.; Stratmann, G. C.; Doshi, R.; Mann, D. M. A.; Harrison, P. J.; Pearson, R. C. A.; Bowen, D. M. beta-Amyloid precursor protein isoforms show correlations with neurones but not with glia of demented subjects. *Acta Neuropathol. (Berl.)* **1994**, *88*(6), 545-552.
- [47] Lovell, M. A.; Ehmann, W. D.; Mattson, M. P.; Markesbery, W. R. Elevated 4-hydroxynonenal in ventricular fluid in Alzheimer's disease. *Neurobiol. Aging* **1997**, *18*(5), 457-461.
- [48] Begni, B.; Brighina, L.; Sirtori, E.; Fumagalli, L.; Andreoni, S.; Beretta, S.; Oster, T.; Malaplate-Armand, C.; Isella, V.; Appollonio, I.; Ferrarese, C. Oxidative stress impairs glutamate uptake in fibroblasts from patients with Alzheimer's disease. *Free Radic. Biol. Med.* **2004**, *37*(6), 892-901.
- [49] Cacabelos, R.; Takeda, M.; Winblad, B. The glutamatergic system and neurodegeneration in dementia: preventive strategies in Alzheimer's disease. *Int. J. Geriatr. Psychiatry* **1999**, *14*(1), 3-47.
- [50] Klyubin, I.; Walsh, D. M.; Cullen, W. K.; Fadeeva, J. V.; Anwyl, R.; Selkoe, D. J.; Rowan, M. J. Soluble Arctic amyloid beta protein inhibits hippocampal long-term potentiation *in vivo*. *Eur. J. Neurosci* **2004**, *19*, 2839-2846.
- [51] Abbott, J. J.; Howlett, D. R.; Francis, P. T.; Williams, R. J. Abeta(1-42) modulation of Akt phosphorylation *via* alpha7 nAChR and NMDA receptors. *Neurobiol. Aging* **2007**, *29*(7), 992-1001.
- [52] Bachman, D.; Rabins, P. "Sundowning" and other temporally associated agitation states in dementia patients. *Annu. Rev. Med.* **2006**, *57*, 499-511.
- [53] Neilsen, H. S.; Georg, B.; Hannibal, J.; Fahrenkrug, J. Homer-1 mRNA in the rat suprachiasmatic nucleus is regulated differentially by the retinohypothalamic tract transmitters pituitary adenylate cyclase activating polypeptide and glutamate at time points where light phase-shifts the endogenous rhythm. *Brain Res. Mol. Brain Res.* **2002**, *105*, 79-85.
- [54] Li, L.; Sengupta, A.; Haque, N.; Grundke-Iqbal, I.; Iqbal, K. Memantine inhibits and reverses the Alzheimer type abnormal hyperphosphorylation of tau and associated neurodegeneration. *FEBS Lett.* **2004**, *566*, 261-269.
- [55] Grimes, C. A.; Jope, R. S. The multifaceted roles of glycogen synthase kinase 3beta in cellular signaling. *Prog. Neurobiol.* **2001**, *65*(4), 391-426.
- [56] De Sarno, P.; Bijur, G. N.; Zmijewska, A. A.; Li, X.; Jope, R. S. *In vivo* regulation of GSK3 phosphorylation by cholinergic and NMDA receptors. *Neurobiol. Aging* **2006**, *27*, 413-422.
- [57] Chan, S. F.; Sucher, N. J. An NMDA receptor signaling complex with protein phosphatase 2A. *J. Neurosci.* **2001**, *21*, 7985-7992.
- [58] Capsoni, S.; Ugolini, G.; Comparini, A.; Ruberti, F.; Berardi, N.; Cattaneo, A. Alzheimer-like neurodegeneration in aged antinerve growth factor transgenic mice. *Proc. Natl. Acad. Sci. USA* **2000**, *97*(12), 6826-6831.
- [59] Ruberti, F.; Capsoni, S.; Comparini, A.; Di Daniel, E.; Franzot, J.; Gonfloni, S.; Rossi, G.; Berardi, N.; Cattaneo, A. Phenotypic knockout of nerve growth factor in adult transgenic mice reveals severe deficits in basal forebrain cholinergic neurons, cell death in the spleen, and skeletal muscle dystrophy. *J. Neurosci.* **2000**, *20*(7), 2589-2601.
- [60] Capsoni, S.; Giannotta, S.; Cattaneo, A. Early events of Alzheimer-like neurodegeneration in anti-nerve growth factor transgenic mice. *Brain Aging* **2002**, *2*(4), 24-43.
- [61] Chohan, M. O.; Khatoun, S.; Iqbal, I. -G.; Iqbal, K. Involvement of I₂^{PP2A} in the abnormal hyperphosphorylation of tau and its reversal by memantine. *FEBS Lett.* **2006**, *580*, 3973-3979.
- [62] Degerman Gunnarsson, M.; Kilander, L.; Basun, H.; Lannfelt, L. Reduction of phosphorylated tau during memantine treatment of Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* **2007**, *24*, 247-252.
- [63] Volavka, J.; Citrome, L.; Huertas, D. Update on the biological treatment of aggression. *Actas Esp. Psiquiatr.* **2006**, *34*(2), 123-135.