Clinical neurochemistry: developments in dementia research based on brain bank material

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Summary. Brain tissue obtained at autopsy continues to provide unique opportunities in current dementia research. Not only is tissue analysis still essential for diagnosis, but investigation of neurochemical pathology, at a level of resolution beyond current in vivo imaging, continues to provide new insights into the involvement of neurotransmitter signalling systems. These are relevant to therapy which, with respect to symptoms such as cognitive impairment, psychosis and depression, is currently targeted to specific transmitter (cholinergic, dopaminergic and serotonergic) systems. This paper focuses on dopaminergic, cholinergic and histaminergic parameters in Alzheimer’s disease (AD), Dementia with Lewy bodies (DLB) and Parkinson’s disease (PD). In the normal striatum the dopamine transporter and D2 receptor exhibit distinct rostral-caudal distributions and D2 binding is affected by genetic polymorphism at the Taq 1A locus. The transporter is reduced in both DLB and PD but not AD, correlating with severity of extrapyramidal dysfunction, and receptor abnormalities are apparent in DLB patients responding adversely to neuroleptics. Striatal nicotine receptors are lost in all 3 disorders, further reduced as a result of neuroleptic medication, and elevated as a result of tobacco use. In the thalamus there are selective reductions in presynaptic cholinergic activity in DLB in the reticular nucleus which relate to symptoms of hallucinations and fluctuating consciousness prevalent in this disorder. In the hippocampus coupling of muscarinic M1 receptors, relevant to response to cholinergic therapy, is impaired in areas most affected by β-amyloid plaques and intact in less affected areas. Analysis of histamine H2 receptors indicates that, despite presynaptic histamine abnormalities in AD, receptor numbers are normal. Such clinically and therapeutically relevant observations on human brain neurochemistry provide a basis for im-
proving therapeutic strategies and prospects of diagnostic in vivo chemical imaging.

**Keywords:** Alzheimer’s disease, dementia with Lewy bodies, Parkinson’s disease, dopamine transporter and receptors, choline acetyltransferase, nicotinic receptor, histamine H2 receptor.

**Introduction**

Research into the neurobiological basis of Alzheimer’s disease (AD) has progressed dramatically across the last 2 or 3 decades from early observations on histopathological, metabolic and neurochemical abnormalities, to genetic and molecular pathological changes. Treatment strategies, by contrast, have evolved more slowly. The only pharmacologically available approach at present is cholinergic. Cholinesterase inhibitors such as Cognex (tacrine) or Aricept (donepezil) benefit a minority of AD patients (Rogers and Friedhoff, 1996). Recent evidence suggests that symptomatic improvement may relate more to psychotic features (e.g. hallucinations) than cognitive impairment. Patients with Dementia with Lewy bodies (DLB), in which Alzheimer pathology, (particularly neurofibrillary tangles) is less prevalent, may be more responsive (Perry et al., 1989; Levy et al., 1994; Cummings and Kaufer, 1996). Moreover there is some evidence that such therapy may additionally be protective (Davis et al., 1995), an observation consistent with the reduced risk of AD and PD (Parkinson’s disease) in tobacco users (Court and Perry, 1994). Therapeutic expectations of anti-amyloidogenic strategies have yet to be realised although there is emerging evidence of the value of anti-inflammatory and antioxidant (vitamin E) agents. Transmitter manipulation is likely to remain an important target for symptomatic therapy in conjunction with some of these other protective approaches. Together with the application of new molecular probes for in vivo chemical imaging of transmitter systems, which has already identified cholinergic abnormalities in AD and PD (Kuhl et al., 1996), in vitro transmitter analysis in human brain tissue continues to be an exciting research area.

In a recent review of the functional consequences of transmitter complexity, Brezina and Weiss (1997) raised the question of how the functioning of the immensely complex network of transmitters, modulators, hormones and other chemical messengers can be analysed, particularly in view of the divergence in the action of a single transmitter (the range of different receptor subtypes for example) and the convergence of different transmitters (in terms of ion channel and second messenger modulation). At this level, there might seem to be little hope of deciphering the role of any particular molecular signal in contributing to behaviour, nor of targeting any particular clinical symptom by manipulating a single system. And yet major mental disorders and symptoms continue to be analysed mechanistically and manipulated pharmacologically in the context of specific systems. Examples include the role of dopamine and 5-HT receptors in psychosis, of 5-HT and noradrenaline transporters in depression, and most recently of acetylcholine in dementia. Possible relationships between the heterogeneity of genetic sequences coding for the relevant