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Review

The nucleus basalis of Meynert: A new target for deep brain stimulation in dementia?

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ABSTRACT

Dementia is a major cause of disability amongst the elderly and represents a serious global health issue. Current treatments for dementia are limited; at best they provide inadequate symptomatic relief. In contrast, there are a plethora of approaches that provide symptomatic relief for abnormalities of movement including surgical approaches. Deep brain stimulation has been used successfully to directly alter processing in neural networks and thereby improve movement functions. Here we describe the anatomy, intrinsic organization and connectivity of the cholinergic nucleus basalis of Meynert, a basal forebrain structure implicated in cognitive functions including memory, attention, arousal and perception. A significant body of evidence suggests that degeneration of the nucleus and its cortical projections underlies the cognitive decline seen in dementia. We review this evidence and postulate that deep brain stimulation to this nucleus may be able to improve specific cognitive functions. This could represent a novel treatment strategy for some dementias in carefully selected individuals. Controlled trials of deep brain stimulation of the nucleus basalis of Meynert for Parkinson's disease dementia and Alzheimer's disease are required to evaluate potential efficacy and the mechanisms of possible cognitive changes.

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1. Introduction

Dementia is a clinical syndrome comprising declining function across a number of cognitive domains including memory, attention, executive function, perception, praxis and language, which are not attributable to delirium or a psychiatric disorder. These features are accompanied by changes in personality and behaviour. These changes interfere with the ability to function in society, causing severe distress to both the patient and their family (American Psychiatric Association, 2000; Bouchard, 2007; McKhann et al., 2011).

Two of the most common etiologic subtypes are Alzheimer's disease (AD) and Parkinson's disease dementia (PDD), although many others exist. AD is characterised clinically by progressive episodic memory impairment, which fails to normalize with cuing or recognition testing (Dubois et al., 2007). PDD on the other hand is predominantly a dysexecutive syndrome (characterised by impaired planning and concept formation) with significant deficits in free-recall memory, fluctuating attention and hallucinations (Emre et al., 2007). The hallmarks of AD pathology are extraneuronal deposits of amyloid β protein and intraneuronal accumulation of hyperphosphorylated tau protein forming neurofibrillary tangles (Braak and Braak, 1991; Jack et al., 2013). In PDD on the other hand fronto-striatal dopaminergic deficits and cortical spread of Lewy bodies (intracellular aggregates of alpha-synuclein protein) are both contributing features (Pagonabarraga and Kulisevsky, 2012). A pathological feature of both dementias however is loss of cholinergic neurons in the nucleus basalis of Meynert (NBM) of the basal forebrain, which may represent a common pathway in the development of these two dementia syndromes.

Dementia is a serious global health issue with an increasing prevalence (Brookmeyer et al., 2011; Llibre Rodriguez et al., 2008; Reitz et al., 2011). It is estimated that 24.3 million people suffer from AD worldwide, and that number is projected to increase to 81.1 million by 2040 (Ferri et al., 2005). Point prevalence estimates of PDD in those with Parkinson's disease range up to 40% (Aarsland et al., 2005; Aarsland and Kurz, 2010; Caballol et al., 2007) and the cumulative prevalence is very high at 75% of those with duration of illness of more than ten years (Aarsland and Kurz, 2010). Such patients have significantly increased morbidity compared to non-demented PD patients (Reid et al., 1996). Both conditions are also associated with significant societal and economic costs, for example the annual costs associated with dementia have been estimated to be between €105.2 billion (Olesen et al., 2012) and €160 billion (Wimo et al., 2011) in Europe, and $183–385 billion in the United States (Thies and Bleiler, 2011).

Despite this, no effective disease-modifying treatment exists for the dementias (Ballard et al., 2011; Ihl et al., 2011). Current management with cholinesterase inhibitors and NMDA-receptor antagonists produces moderate symptomatic improvement at best (Aarsland et al., 2009; Emre et al., 2010, 2004; Qaseem et al., 2008). Novel therapeutic options are therefore needed. Trials of both vaccination and encapsulated cell biodelivery of growth factors in AD are ongoing, although without breakthrough so far (Eriksdotter-Jönhagen et al., 2012; Karran, 2012; Wahlberg et al., 2012).

Deep brain stimulation (DBS) is an established and effective treatment for movement disorders such as PD, dystonia and essential tremor (Deuschl et al., 2011; Vidailhet et al., 2012; Williams et al., 2010). It has also recently shown promise in the treatment of neuropsychiatric conditions such as Gilles de la Tourette syndrome, obsessive–compulsive disorder and depression (Ackermans et al., 2011; Blomstedt et al., 2012; Lozano et al., 2012). Converging evidence indicates that distributed neural networks control a range of normal cognitive functions, such as the cortico-subcortical loops of the frontoparietal attention network (Bentley et al., 2011; Sarter et al., 2006), and dysfunction at specific key nodes may have profound consequences (McIntyre and Hahn, 2010). Within these networks the nucleus basalis of Meynert plays a major role in modulating widespread cortical cognitive functions. In this paper we begin by reviewing the anatomy, organization, connectivity, pharmacology and functions of the NBM, and the evidence for involvement of this structure in the cognitive decline of dementia. With this in mind we highlight the scientific rationale behind the potential use of DBS of the NBM as a novel treatment for dementia.

2. The nucleus basalis of Meynert: structure, connectivity and pharmacology

2.1. Structure: anatomy and histology of the NBM

Theodor Meynert first described a group of magnocellular hyperchromic neurones located in the human basal forebrain in 1872, naming it the nucleus of the ansa lenticularis (Meynert, 1872). Kölliker later renamed it the nucleus basalis of Meynert (Kölliker, 1896). Detailed human anatomical studies show that the NBM is a flat, nearly horizontal structure extending from the olfactory tubercle anteriorly to the level of the uncal hippocampus at its most caudal extent, spanning a distance of 13–14 mm in the sagittal plane. It reaches its greatest cross-sectional diameter under the anterior commissure in a region known as the substantia innominata, with a medio-lateral width of 16–18 mm (Mesulam and Geula, 1988). In its anterior portion the nucleus is limited inferiorly by the horizontal limb of the nucleus of the diagonal band of Broca, supero-medially by the ventral globus pallidus, and supero-laterally by the lateral extension of the anterior commissure (Figs. 1 and 2). In its posterior portion it abuts the ansa lenticularis superiorly, the putamen laterally, the posterior tip of the amygdala inferiorly, and the optic tract medially (Fig. 2) (Mesulam and Geula, 1988; Rossor et al., 1982). There are striking interspecies differences in the anatomy of the NBM; according to comparative anatomy studies by Gorry (1963) the NBM in rodents is rudimentary and considerably interdigitated with the globus pallidus, whereas in primates and humans the nucleus attains its greatest developments in size as well as differentiation from surrounding cell groups. This may be explained by the massive expansion of the cortical mantle in higher species, which is the main innervation target of the NBM (Divac, 1975; Gorry, 1963).

Immunocytochemical analysis of the human NBM indicates the total number of neurons is approximately 210,000 per hemisphere (Gilmor et al., 1999). Histologically there is a predominance of magnocellular hyperchromic neurons containing conspicuous nucleoli and predominant lipofuscin causing displacement of the nuclei (Mesulam and Geula, 1988). These are fusiform to multipolar in shape and 40–50 μm × 60–70 μm in size (Mufson et al., 2003). There is no characteristic pattern of dendritic arborisation with the dendritic trees of adjacent neurons overlapping and lacking a common orientation (Mesulam and Geula, 1988). Staining shows that 90% of all NBM neurons are choline acyl-transferase (ChAT) positive, and therefore cholinergic, although smaller non-staining galaninergic and GABAergic neurons are also present (Gritti et al., 1993; Mesulam and Geula, 1988; Mufson et al., 2003). The heteromorphic shapes and isodendritic morphologies of NBM neurons have lead some to suggest that they constitute a telencephalic extension of the brainstem reticular formation (Mesulam et al., 1983) since very similar neuronal morphologies are seen there (Ramón-Moliner and Nauta, 1966). Interestingly both areas are thought to be involved in cortical activation and alertness (see below) (Fuller et al., 2011; Saper et al., 2005). Based on cytoarchitectonics, cytochemistry and connectivity patterns Mesulam et al. (1983), Mesulam and Geula (1988) designated NBM neurons as

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