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C-type natriuretic peptide in Parkinson's disease: reduced secretion and response to deprenyl

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Abstract C-type natriuretic peptide (CNP) is a neurotrophic factor widely expressed in the central nervous system including the basal ganglia, limbic system and hypothalamus. Nothing is known of CNP's role in the human brain but in rodents CNP promotes axon growth and branching, and interacts with dopaminergic function in models of addiction. Because preliminary evidence showed reduced levels in Parkinson's disease (PD), we examined concentrations of CNP peptides in cerebrospinal fluid (CSF) in 146 PD patients from the DATATOP study to determine changes over time in relation to medication status and cognitive function. CNP and an aminoterminal product of proCNP (NTproCNP) were measured in extracts from stored CSF by radioimmunoassay. CSF samples were obtained twice—at enrolment and at the study's endpoint (requirement for levodopa treatment) after treatment with placebo or deprenyl. At enrolment, median baseline concentration of CSF NTproCNP (776 pmol/L, $n = 146$) was significantly lower than that in a reference group without neurological disorder (1,010 pmol/L, $p < 0.001$). Concentrations declined significantly during placebo ($p = 0.02$) and lower values at enrolment were associated with more rapid functional decline ($p < 0.01$). In contrast, deprenyl—a treatment which delayed the need for levodopa—nullified the time-dependent decline in CSF NTproCNP. In conclusion subnormal CSF NTproCNP which declines with time and associates with increasing functional disability implicates CNP in PD. Concordant clinical and peptide responses to deprenyl suggest that some of the benefits of monoamine oxidase inhibitors in PD are mediated by preserving tissue CNP activity.

Keywords Parkinson's disease · CSF · NTproCNP · Monoamine oxidase inhibitors

Introduction

C-type natriuretic peptide (CNP) belongs to a family of peptides best known for their actions within the cardiovascular system (Potter et al. 2006). Unlike its close relatives (Atrial Natriuretic Peptide and B-type Natriuretic Peptide), CNP is expressed in many other tissues where its largely paracrine actions, mediated by CNP's unique receptor NPR-B, regulate cell growth and maturation (Potter et al. 2006). CNP signalling pathways have been identified throughout the brain and spinal cord, and are enriched in the basal ganglia, limbic system and hypothalamus (Komatsu et al. 1991; Herman et al. 1996; Langub et al. 1995). CNP pathway activity is especially prominent in regulating perinatal stages of brain maturation (Muller et al. 2009, 2010) and promotes neuronal growth (Zhao and Ma 2009) and synaptic plasticity in hippocampal tissues (Decker et al. 2010). Recently, natriuretic peptides were shown to potently inhibit presynaptic glutamate

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release in murine epithalamic and subcortical nuclei (Hu et al. 2012). Collectively, this evidence raises the possibility that loss of CNP activity may also influence the course of neurodegenerative disorders in humans.

Nothing is known of the role or regulation of CNP in the human brain but there is reason to suspect that the peptide is implicated in Parkinson's disease. In genetic studies where the CNP receptor has been disrupted, disorders of locomotion—with the addition of central priapism—resulted (Tamura et al. 2004). Interactions with dopaminergic pathways are suggested by strong co-location of peptide and the NPR-B receptor within the subthalamic nuclei and basal ganglia (Thiriet et al. 2001). Moreover, the CNP receptor is co-located in neurons expressing tyrosine hydroxylase and interacts with dopaminergic function in models of cocaine addiction (Jouvert et al. 2004). CNP is synthesized as the prohormone (proCNP) which is processed intracellularly to yield the bioactive form (CNP 53) (Wu et al. 2003) and a stable (bio-inactive) component, amino terminal proCNP (NTproCNP) (Prickett et al. 2001). Both are secreted in equimolar concentrations but NTproCNP provides a better index of the hormone's production because CNP is rapidly degraded (Kenny et al. 1993; Hunt et al. 1994). In preliminary studies, we have found significantly reduced concentrations of NTproCNP in cerebrospinal fluid (CSF) in Parkinson's disease patients compared with those measured in age-matched subjects without neurological disorder. Here we have examined CNP and NTproCNP extracted from lumbar CSF samples of Parkinson's disease patients collected on two occasions during the DATATOP trial (Parkinson Study Group 1989a, b). Hypothesising that CNP peptides in CSF drawn from subjects with Parkinson's disease will (1) be subnormal at enrolment and fall further during placebo treatment and (2) will relate to cognitive impairment and disease severity, we have related the findings to clinical scores and treatment regimens. Because treatment with deprenyl (selegiline), a selective and irreversible inhibitor of monoamine oxidase type B, in the DATATOP study selectively delayed functional decline, the effect of this drug on CSF CNP peptides was also examined.

Methods

In 1987 the DATATOP clinical trial was initiated to evaluate the efficacy of deprenyl and alpha tocopherol (Vit E) in delaying the progression of Parkinson's disease. Details of this study have been previously reported (Parkinson Study Group 1989a, b). In this DATATOP trial, 800 previously untreated subjects with clinically confirmed idiopathic Parkinson's disease of recent onset (<5 years) were studied over a 2-year period after randomising to one of four treatment arms: placebo, Vit E, deprenyl or combination of both drugs. The primary objective of the study was to establish the time at which functional decline necessitated commencement of levodopa (endpoint). In all subjects, a sample of lumbar cerebrospinal fluid (CSF) was taken at enrolment, and a second sample obtained at endpoint or—if subjects did not deteriorate sufficiently to warrant levodopa—at the study's completion (approximately 24 months after enrolment). Some of the latter group volunteered to participate in an extension of the trial (DATX) (Parkinson Study Group 1993, 1996), during which subjects originally assigned to placebo or Vit E arms of DATATOP also took deprenyl. In these subjects, the second CSF sample collection was deferred until endpoint was met or the trial was completed. Clinical evaluations using standardised protocols [including Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr staging, Mini-Mental State Examination and Hamilton Depression Scale (HDS)] were undertaken at baseline and at intervals of 3 months excepting the HDS which was evaluated 6 monthly. The 2-year DATATOP study was later extended for a further 5-year period of evaluation (Shoulson et al. 2002; Uc et al. 2009).

Subject selection for CSF sampling

To address the stated hypotheses, CSF samples from the DATATOP study were sought from subjects in the placebo arm of the trial (Study 1), and from a larger group—irrespective of allotted treatment—selected according to cognitive status (Study 2). CSF samples from a small group of Parkinson's disease subjects in Christchurch (outside the DATATOP trial), served as controls for differences in sample collection and storage (details below). CNP levels from CSF of 51 subjects (mean age 70 years) without neurological disorder were used as a reference.

Placebo arm (Study 1)

Suitable samples of CSF, available at two time points in the DATATOP study (at enrolment and at endpoint or study completion) in 58 Parkinson's disease subjects, were the substrate for study of associations of CNP peptides with clinical evaluation and disease progression in the absence of anti-Parkinson medication.

Effect of severity and cognition status (Study 2)

In order to study associations of CSF CNP peptides with changing cognition—irrespective of treatment arm—we first defined three groups [with either dementia (PD-D), mild cognitive impairment (PD-MCI) or normal cognition (PD-N); Supple 1].

Christchurch Parkinson's disease Study

Analyses of CNP peptides in freshly drawn CSF collected from 11 subjects with Parkinson's disease served as a check on possible effects of prolonged storage in DATATOP collections. These subjects were participating in a Christchurch study on the clinical benefits of an oral preparation of anthocyanins (inhibitors of reactive oxidation species). All but one of these subjects were on anti-Parkinson's medication (levodopa in 9, MAO inhibitor in 1) at the time of the initial CSF sampling.

CSF collection, CNP assays and validation of DATATOP samples

CSF was obtained by lumbar puncture after an overnight fast and stored frozen without preservative at −70 °C in alarmed freezers until requested, then transported frozen on dry ice for subsequent analysis at Endolab Christchurch New Zealand. CNP and NTproCNP were assayed in CSF samples as previously described (Schouten et al. 2011) (Supple 2). Supple 3 and 4 provide evidence validating the use of CSF samples after prolonged storage, and the effects of CSF volume withdrawal on CNP concentrations, respectively. All measurements of CNP peptides were performed in the same laboratory using standardised conditions of quality control.

Statistical analyses

Unless otherwise indicated, results are expressed as median (interquartile range). Spearman rank coefficient was used to determine correlations between variables, presented as r values. Kruskal–Wallis one way analysis of variance on ranks was used to compare study groups followed by Dunns test for multiple comparisons. Statistical significance was assumed when $p < 0.05$.

Protocol approval and patient consent

The DATATOP study and its extensions had been approved by Institutional Review Boards of all participating Institutions. The Christchurch study was approved by the Southern Community Ethics Committee and informed consent was obtained in all subjects prior to study.

Results

Christchurch study of Parkinson's disease

In 11 subjects (all male), median age was 70 years, (range 48–80). Duration of disease was <5 years (median duration of symptoms 3 years). Median UPDRS was 33 (no disability 0, severe disability 56).

Median CSF concentration of CNP and NTproCNP (Fig. 1) was 8.6 (7.7–9.8) pmol/L and 677 (592–785) pmol/L, respectively. Median ratio of NTproCNP/CNP was 80 (68–98) No significant association with duration or severity of the disease was found in this small group but the ratio NTproCNP/CNP was positively linked with age ($r = 0.83$, $p < 0.001$).

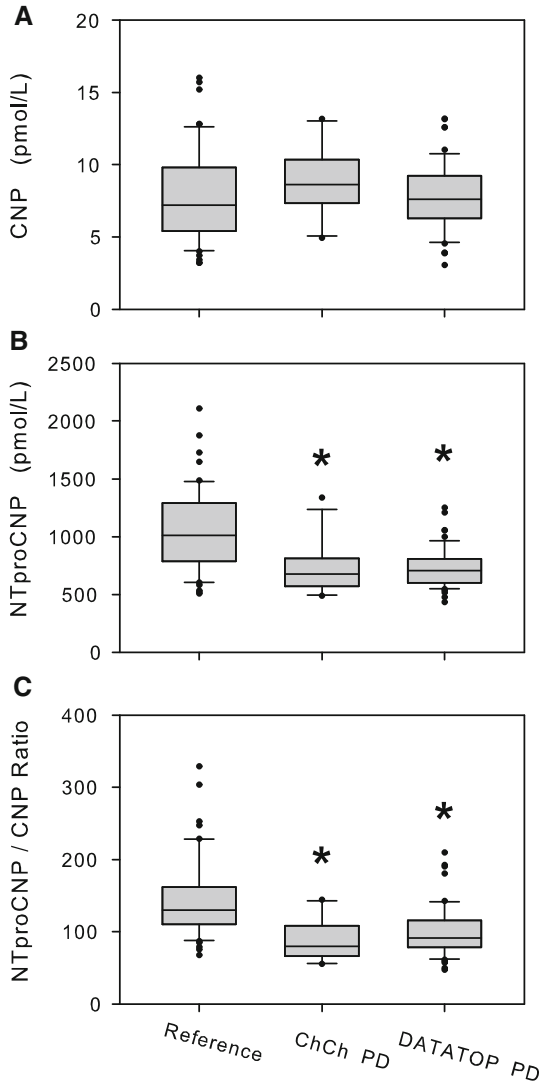

Fig. 1 Plot of CSF concentrations of CNP (**a**), NTproCNP (**b**) and NTproCNP/CNP ratio (**c**) in 3 different populations. *Reference*; data from subjects with no neurological disorder ($n = 51$); *ChCh PD* Christchurch subjects with confirmed Parkinson's Disease (PD, $n = 11$); *DATATOP PD* untreated subjects ($n = 58$). *Box plots* show median (*horizontal line*), 25th and 75th percentiles (*box*), and 10th and 90th percentiles (*error bars*). *Dots* identify outliers. Significant differences from reference data set are indicated by *asterisks* (*$p < 0.05$)

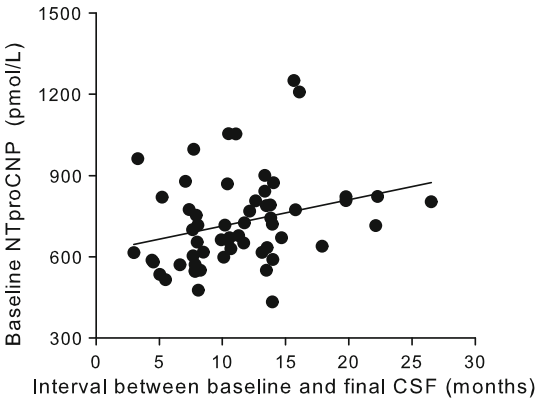

Fig. 2 Relationship between baseline NTproCNP concentration and the time interval between CSF collections in Study 1. Line fitted by Least Squares method

DATATOP samples, placebo arm (Study 1)

In the 58 subjects studied (21 females), median age was 64 years (57–68 years). Median duration of symptoms prior to CSF sampling was 20 months. Median UPDRS at enrolment was 29 (23–40).

At baseline, median CSF CNP and NTproCNP concentrations (Fig. 1) were 7.6 (6.3–9.2) pmol/L and 707 (606–807) pmol/L, respectively; NTproCNP/CNP ratio was 91 (80–115). Concentrations of CNP and NTproCNP were correlated ($r = 0.26$, $p = 0.05$). Compared to the local reference age-matched population without neurological disorder (Schouten et al. 2011), NTproCNP and NTproCNP/CNP ratio were both lower ($p < 0.05$) in Parkinson's disease subjects—whether samples were stored for prolonged periods (DATATOP) or measured soon after collection (Christchurch samples; Fig. 1). Values did not differ significantly according to age or gender. Among subjects, there were 3–5 fold differences in concentration of either peptide but no association was found with disease duration, phenotype or severity as determined at baseline.

At follow-up, median CSF CNP and NTproCNP concentrations were 7.6 (5.6–8.9) pmol/L and 692 (570–842) pmol/L respectively; NTproCNP/CNP ratio was 95 (76–119). Again, CNP and NTproCNP concentrations were correlated ($r = 0.36$, $p < 0.01$). As noted at baseline, no associations of CSF CNP peptides were identified with either phenotype or severity. Similarly, no link was found between change in CSF concentrations and clinical status.

There was a significant positive association of baseline NTproCNP with the time interval separating CSF collections ($r = 0.34$, $p < 0.01$)—lower values at baseline qualified for earlier treatment intervention (Fig. 2).The median time interval between CSF sampling—determined by the need to institute specific treatment—was 11 (8–14) months. As shown in Fig. 3a, CSF NTproCNP concentration declined significantly over time in these placebo-treated subjects ($r = -0.31$, $p = 0.02$).

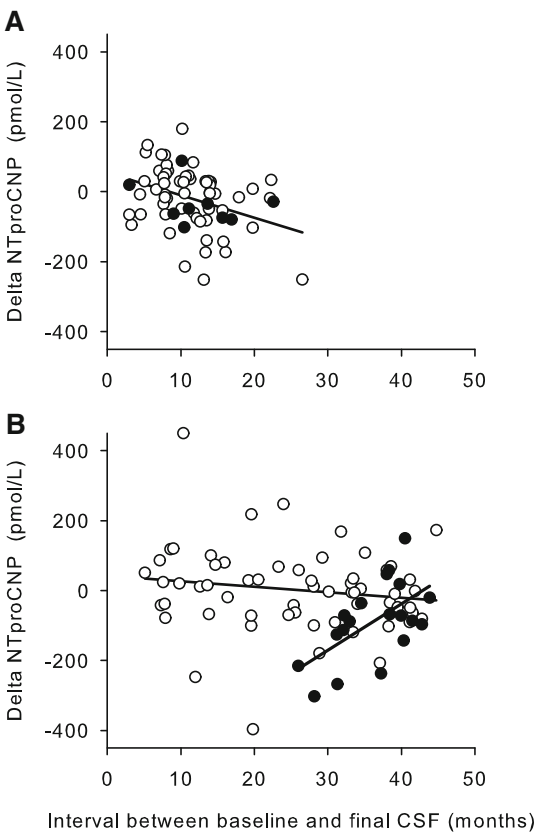

Fig. 3 **a** Relationship between the change (delta, final minus baseline) in NTproCNP concentration and the time interval between CSF collections in Study 1 (*open circles*) and subjects in Study 2 who did not receive deprenyl at any stage (*closed circles*). **b** Relationship between the change (*delta*) in NTproCNP concentration and the time interval between CSF collections in Study 2 for subject who received deprenyl (*open circles*) and subjects who only received deprenyl following completion of Study 1 (*closed circles*). *Lines* for *open* and *closed symbols* fitted by Least Squares method

DATATOP samples and cognition (Study 2)

Based on results of neuropsychological testing at final follow-up assessment (up to 7 years after enrolment), and CSF availability, we selected baseline and follow-up CSF samples from 88 subjects—31 judged to have PD-D, 28 with PD-MCI and 29 with PD-N. Included in the group were 56 subjects who had not attained endpoint within the original DATATOP trial and who agreed to participate in its extension (DATX). As illustrated in a representative example in Fig. 4 good discrimination of cognitive status was obtained across the three groups. Despite the clear differences in cognition, CSF concentrations of CNP peptides did not differ among groups (Fig. 5)—either at baseline or at follow-up CSF sampling. Combining results

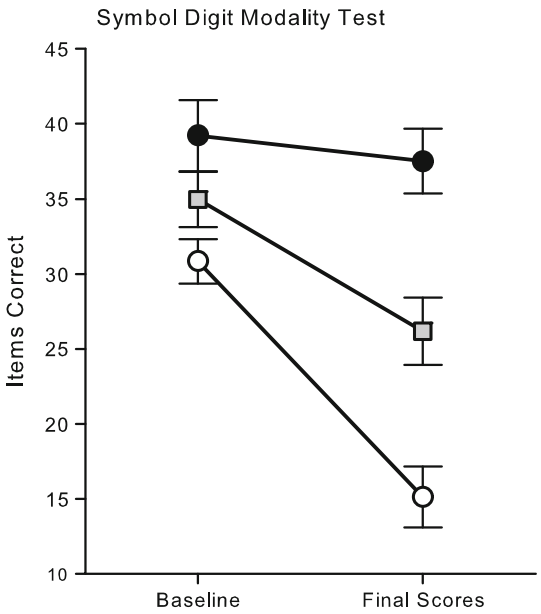

Fig. 4 Performance (mean ± SE) in the Symbol Digit Modality Test among 88 subjects at baseline (enrolment) and at final assessment. The mild cognitive impairment group (PD-MCI, *grey squares*) and especially the dementia group (PD-D, *open circles*) showed a steep decline in performance across time, unlike the patients showing normal levels of cognitive ability (PD-N, *filled circles*)

from all 3 groups ($n = 88$), median peptide concentrations at baseline [(CNP 9.1 (7.4–10.7) pmol/L, NTproCNP 860 (673–1,027) pmol/L and ratio 94 (75–112)] did not differ significantly from follow-up values [CNP 8.4 (6.9–9.8) pmol/L; NTproCNP 836 (662–999) pmol/L; ratio 95 (78–124)]. As in the placebo Study 1, at both time points CSF CNP and NTproCNP were strongly correlated with respective follow-up values ($r = 0.66$ and 0.85 respectively, $p < 0.0001$). At both time points the NTproCNP/CNP ratio was significantly positively associated with age ($r = 0.27$ for baseline, 0.26 at follow-up, $p < 0.05$). No significant associations of peptide levels were identified with other clinical scores including UPDRS and HDS, either at baseline or at the time of the second CSF collection.

Time-dependent changes in CSF NTproCNP

Unlike the time-dependent decline in CSF NTproCNP observed in Study 1, we found no such trend in the 88 subjects selected on the basis of cognition. Hypothesising that this difference could be treatment-dependent (for example affected by deprenyl which in the same DATATOP study was shown to delay functional decline) we analysed changes in peptide concentrations according to administered treatments. Of the 88 subjects, 60 had been randomized to receive deprenyl with or without Vit E. As shown in Fig. 3b (open symbols), in these subjects there

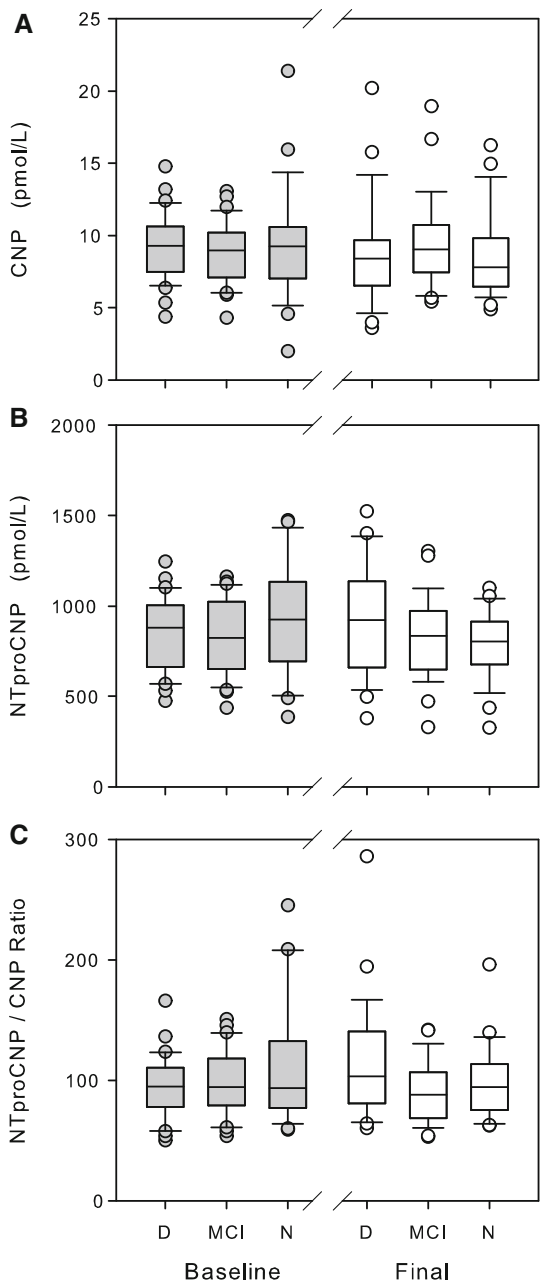

Fig. 5 CSF concentrations of CNP (**a**), NTproCNP (**b**) and NTproCNP/CNP ratio (**c**) at baseline (*left*) and final CSF draw (*right*) in three cognitive groups—normal (N), mild cognitive impairment (MCI) and dementia (**d**). *Box plots* show median, 25th and 75th percentiles, and 10th and 90th percentiles. *Circles* indicate outliers

was no significant decline in CSF NTproCNP despite the extended time separating CSF sampling. The change in CSF NTproCNP for19 subjects assigned to receive placebo and/or Vit E in the original study, but who did not endpoint and therefore qualified for addition of deprenyl in the extended study (Parkinson Study Group 1996), are shown in Fig. 3b (closed symbols). In these subjects the decline in CSF levels was progressively mitigated by increasing duration of

deprenyl treatment. In the 9 subjects reaching endpoint in the placebo and/or Vit E arms (and therefore never receiving deprenyl), levels declined with time (Fig. 3a, closed symbols, $r = -0.28$) as found in the placebo study above.

Discussion

In this first report of CNP peptides in cerebrospinal fluid in Parkinson's disease, we show that the concentration of NTproCNP—a stable product of CNP production in tissues—is reduced in untreated subjects at enrolment and falls further in subsequent months. Moreover, lower levels at baseline are associated with more rapid functional decline. Unexpectedly we find that the MAO inhibitor, (deprenyl), a treatment previously shown to delay the need for levodopa in these DATATOP subjects, also nullifies the time-dependent fall in CSF NTproCNP. These novel observations suggest that CNP production is modulated in Parkinson's disease and may confer a neuroprotective benefit which now needs to be further explored.

CNP transcripts and components of the CNP signalling pathway are found throughout the CNS (Herman et al. 1996; Abdelalim and Tooyama 2011). In keeping with this, concentrations of bioactive (CNP 53 and CNP 22) and bio-inactive (NTproCNP) forms are increased in CSF collected from normal humans (Schouten et al. 2011), far exceeding concentrations found in the systemic circulation (Schouten et al. 2011). In health, the ratio of NTproCNP to CNP in CSF is some fivefold higher than in plasma—findings consistent with increased degradation and/or clearance of CNP by neural tissues within the blood brain barrier. Since both CNP and NTproCNP are likely to be secreted in equimolar proportions, measuring NTproCNP in CSF provides a more valid marker of tissue CNP production—especially as CNP degradation rates are likely to change in specific disease states. Neprilysin activity, which rapidly degrades CNP (Kenny et al. 1993), is reduced in neurodegenerative disorders (Kakiya et al. 2012) including Parkinson's disease (Llorens-Cortes et al. 1984), and may explain our findings of reduced NTproCNP/CNP ratio in the presence of unchanging CNP. Together with reduced concentrations of NTproCNP, the findings support a fall in CNP production and clearance in Parkinson's disease. Values of NTproCNP in a large group of DATATOP untreated Parkinson's disease subjects, and in a small group of Parkinson's disease subjects stabilized on treatment, were significantly lower than values drawn from a reference age-matched population without neurological disorder (Schouten et al. 2011). Combining all baseline values in the 2 DATATOP studies (total 146 subjects) median NTproCNP [776 (630–958) pmol/L] was significantly lower than the reference group [51 subjects, 1,010 (788–1,292) pmol/L, $p < 0.001$]. This previously unreported finding is independent of drug therapy or cognition and could be a novel signature of Parkinson's disease. A recent study (Koziorowski et al. 2012) reports that NTproCNP concentrations in the systemic circulation are raised in subjects with long standing Parkinson's disease receiving daily L Dopa treatment. Since concentrations of CNP peptides in CSF and plasma appear to be independently regulated—at least in subjects without neurological disorders (Schouten et al. 2011)—the relevance of these findings to the current observations is unclear. Further, in the Christchurch study of early onset Parkinson's disease where CSF levels were clearly subnormal (see Fig. 1), we found concurrent levels of plasma NTproCNP (measured by our fully validated and published RIA) were in fact lower than age-matched controls.

Although no association was found with UPDRS, reduced CNP production may be an early manifestation of an underlying disorder of motor function. Of note, the range of peptide concentrations (3-5 fold variation among subjects) was similar to that found in those without neurological disorder (Schouten et al. 2011). The source of this variation—which closely replicates on re-sampling—is unknown but in the current study is unlikely to be related to disease duration, severity or phenotype as determined by clinical scores and ratings recorded in the DATATOP study. Nonetheless, the fact that subjects developing disabling features early in the trial exhibit lower concentrations of NTproCNP at baseline (Fig. 2) suggests that CNP production within the brain connects with a global measure of functional decline that is not captured by the standardised clinical tests in current use. Consonant with this finding is the time-dependent fall in CSF NTproCNP (Fig. 3a) in untreated subjects. Since age *per se* is not linked with CSF NTproCNP concentrations—either in the current study or in the reference population (Schouten et al. 2011)—the fall is likely to be intrinsic to Parkinson's disease.

Our second major objective—exploring any association of CNP peptides with cognition in Parkinson's disease subjects—was addressed by selecting appropriate subjects from the DATATOP study irrespective of treatment. We are confident that, in selecting the 3 groups, we successfully stratified changing cognitive status during the period of review as shown by the differential changes in the measured variables up to 5 years after the second CSF collection. However since CSF concentrations of CNP peptides did not differ among the three groups, nor was change in value associated with cognition status, we conclude that the CSF concentration of these peptides does not predict subsequent cognitive impairment in later years.

The finding that a time-dependent fall in NTproCNP occurs in placebo-treated subjects (Study 1) prompted us to examine the impact of treatment on peptide changes in CSF in the 88 subjects selected for study of associations with cognitive status. With the exception of proportions with impaired cognition (which as shown above does not affect peptide levels), this population was similarly matched to those in Study 1. Distinct from the observations made in the placebo group, subjects receiving deprenyl (with or without vitamin E) showed no decline in CSF NTproCNP concentrations—despite a longer time interval separating CSF sampling. Extension of the trial for those not attaining the DATATOP endpoint provided the opportunity to examine peptide responses to later commencement of deprenyl (Fig. 3b). In those who had not been assigned to receive deprenyl, its later implementation progressively attenuated the decline in CSF NTproCNP despite the much longer interval separating CSF sampling (mean 36 months) during which (in the absence of deprenyl) further decline would be expected. In contrast, CSF NTproCNP declined in subjects assigned to placebo and/or Vit E and who did endpoint—as noted in Study 1 subjects (Fig. 3a).

Findings of subnormal CSF NTproCNP concentrations which decline with time and associate with increasing functional disability, together with concordant clinical and peptide responses in subjects receiving deprenyl, provide strong evidence implicating CNP production in Parkinson's disease. However the mechanism underlying the increased levels in deprenyl-treated subjects—and any biological significance—remain to be clarified. To our knowledge, none of the neuroamine products of MAO B inhibition is known to up regulate CNP gene expression but this now warrants further study. Alternatively, it is possible that deprenyl selectively affects metabolism or clearance of NTproCNP from CSF, although the time course of the NTproCNP response makes this unlikely. Biological significance is suggested by the conjunction of increasing NTproCNP with the time-sparing benefits of deprenyl. Moreover, the findings suggest that some of the actions of MAO inhibitors in Parkinson's disease are mediated by preserving tissue CNP activity. Of note, CNP increases expression of several neurotrophic factors that inhibit apoptosis in retinal ganglion cells (Ma et al. 2010), and similarly prolong survival in PC12 cells (Fiscus et al. 2001). These and other neuroprotective actions of CNP—including enhanced differentiation of proliferative neurons (Simpson et al. 2007), stimulation of catecholamine production in PC12cells (Takekoshi et al. 2000) and CNP's supporting role in glial tissue (Prado et al. 2010)—all deserve consideration. Clearly further advances will depend on a more detailed understanding of CNP gene regulation and its effects within brain tissues both in normal physiology and in neurodegenerative disorders.

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Conflict of interest The Authors have nothing to declare.

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