Central nervous system functions in familial neurohypophysial diabetes insipidus

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Introduction

Familial neurohypophysial diabetes insipidus (FNDI) is caused by a deficiency of the hormone vasopressin as a result of a heterozygous mutation in the vasopressin prohormone gene and is characterized by polydipsia and polyuria. Till now over 40 different mutations have been identified all having the same major effect on diuresis (1). The disease generally is not manifest during the first months or years of life but develops progressively thereafter (2). The delayed onset indicates that the mutant prohormone gradually induces the lack of vasopressin secretion despite the presence of the normal allele. It causes growth retardation as a result of a decrease in food intake and so affects growth and development when the disease starts at birth and is initially unnoticed (3). FNDI mutant prohormones are retained in the endoplasmatic reticulum (ER). It has been found that large accretions are formed in cells expressing FNDI prohormones (3) and it has been indicated that these might also be formed in magnocellular neurons expressing the Cys116Gly mutant. This could result in severe dysfunction of the cell, and even cell death. This is supported by post-mortem and MRI studies, which show that magnocellular nuclei are degenerated (2).
Vasopressin is synthesized in, transported within and secreted from multiple distinct classes of neurons (4). Magnocellular neurons in the hypothalamus, from where it is transported to and stored in the posterior pituitary from where the hormone is released into the general circulation. Parvocellular vasopressin containing cells are found in the hypothalamus as well as in extrahypothalamic sites and constitute different anatomical and functional vasopressin systems in the brain, like neuroendocrine regulation of the pituitary gland, circadian regulation of brain function (4).
Animal experiments during the last 4 decades revealed that besides the peripheral endocrine effects, vasopressin also regulates numerous brain functions, like learning and memory processes, aggression, social, sexual, maternal and rewarded behavior, the regulation of the autonomic nervous system, the cardiovascular system and body temperature. These effects are probably mediated by the parvocellular vasopressin containing nerve fibres, which project to midbrain limbic structures and this could be affected in FNDI (4, 5).
Vasopressin exerts a long-term-effect on learning and memory processes, facilitates consolidation as well as retrieval processes and prevents and reverses retrograde amnesia (4, 5).
Several human studies, in particular those of the pioneering work of De Wied and co-workers, showed that vasopressin- and related peptides are involved in memory processes and learning (6, 7).

Methods

We have previously identified a Dutch family suffering from FNDI due to heterozygosity for the normal allele and a T>G transition mutation at nucleotide 2110 (codon 116) of the mutated allele. The mutation encodes a cysteine-glycine substitution at amino acid 116 of the AVP-NP II gene (8).
Our finding of this family with a large number (50%) of FNDI positive members (8) made it possible to compare cognitive and other CNS effects in these subjects with those of the negative members of the same family, as well as with healthy (non-family member) individuals.
A total of 37 adult volunteers (Cys116Gly positive and negative) of the same FNDI family and 11 non-family members were neuropsychologically tested during a two-hour session by the same neuropsychologist. Exclusion criteria were brain damage or related traumas, such as whiplash-associated disorders; neurological diseases; use of medication with side-effects on cognitive functioning (2 FNDI positive subjects used 1-deamino-D-arginine-vasopressin medication but this treatment was stopped 1 week before neuropsychological testing); regular alcohol abuse; behavioral disorders. For neuropsychological assessment, well-known, internationally published tests were used (9). Some tests were specifically designed for testing Dutch-speaking subjects. The subjects were tested for motivation, premorbid intelligence, attention and executive functions, organization and planning and memory functions. They also had to fill in some questionnaires.

Results

Most of the patients were seen when they consulted the endocrinologist. Subjective findings for FNDI positive subjects were that they showed corresponding characteristics in behavior, attention and concentration. Some of them showed forgetfulness, especially when specific information (e.g. telephone numbers) was asked.

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Table 1. Various neuropsychological parameters in FNDI positive and control subjects. *: independent 2-samples t-test.

Neuropsychological parameter	Controls (n = 25)	FNDI positives (n = 23)	Sign*
Premorbid intelligence	75.2±11.6	73.0±13.5	NS
Short-term memory	0.80±1.0	0.9±1.0	NS
Digit span (OLS statistics: t: -0.158; df: 46; P: NS)			
Forward counting	5.7±3.0	6.3±1.7	NS
Backward counting	5.6±1.6	5.1±1.8	NS
Sum of forward and backward counting	10.9±3.6	11.4±2.9	NS
Arithmetics to measure speed of (OLS statistics: t: -1.520; df: 46; NS)			
Calculation	9.2±3.5	10.7±2.8	NS
Calculation in decile score	4.0±1.8	4.5±1.4	NS
Errors during calculation	0.8±1.1	0.6±0.7	NS
Auditory verbal learning test (15 words test) (OLS statistics: t: 1.627; df: 46; NS)			
Number of stored words in trial 1	5.5±1.4	4.9±1.7	NS
Number of stored words in trial 2	8.2±2.0	7.4±1.6	NS
Number of stored words in trial 3	9.5±1.9	8.8±2.1	NS
Number of stored words in trial 4	10.5±2.4	10.0±1.9	NS
Number of stored words in trial 5	11.2±2.2	10.9±2.0	NS
Total number of words stored and reproduced	44.8±8.3	42.1±7.4	NS
Number of incorrect words reproduced	1.2±1.7	1.8±2.0	NS
Word retrieved from long-term memory	9.4±2.6	9.0±2.0	NS
Failure to retrieve words from long-term memory	6.4±3.3	8.5±2.8	0.05
Words recognized correct from distractor words	14.6±0.6	14.0±1.7	NS
Visual construction and visual memory (OLS statistics: t: 0.788; df: 46; NS)			
Copy of a complex figure	33.9±2.6	32.2±4.6	NS
Organization and planning of the figure	6.8±5.8	8.0±5.7	NS
Recall of the figure without recall instructions	18.7±7.0	19.2±6.0	NS
Number of omissions (part of the figure)	7.1±7.4	5.5±2.8	NS
Divided attention (OLS statistics: t: 0.836; df: 46; NS)			
Part A (s)	37.0±11.5	36.6±12.8	NS
Part B (s)	33.5±10.0	37.3±16.9	NS
Part C (s)	53.2±15.2	56.7±21.5	NS
Number of errors in part C	0.2±0.5	0.3±0.9	NS
Selective attention (OLS statistics: t: 0.998; df: 46; NS)			
Time needed to read words (s)	46.2±15.0	42.0±5.2	NS
Time needed to read colors(s)	54.8±11.9	52.5±9.2	NS
Interference measure (s)	33.5±15.1	34.8±12.1	NS
Errors made during interference measurement	1.7±2.5	2.5±2.7	NS
Verbal fluency (OLS statistics: t: 620; df: 46; NS)			
Total score of animals and professions	45.6±13.0	43.7±9.0	NS
C-score based on age and gender	6.4±1.6	6.1±1.2	NS
Sustained attention (OLS statistics: t: 2.660; df: 46; P < 0.05)			
Mean time to complete part 1 (s)	12.4±1.6	13.4±2.4	NS
Mean time to complete part 2 (s)	12.3±1.6	14.0±2.4	0.01
Fluctuations in part 1	1.1±0.3	1.2±0.4	NS
Fluctuations in part 2	1.2±0.5	1.3±0.4	NS
Omissions in part 1	5.4±5.0	10.8±9.0	0.05
Omissions in part 2	8.1±5.6	10.9±8.7	NS
Symptom check list (self report) (OLS statistics: t: 0.092; df: 46; NS)			
Anxiety	12.3±3.1	12.7±3.0	NS
Agoraphobia	7.6±1.0	7.1±0.3	0.01
Depression	21.1±6.3	21.0±7.0	NS
Somatic complaints	15.2±3.9	17.2±5.1	NS
Insufficiency	12.9±3.3	13.8±3.8	NS
Sleeping disorders	4.0±1.7	4.7±2.3	NS
Miscellaneous complaints	11.1±2.3	9.8±1.6	0.05
Total score of psychoneuroticism	115.2±21.8	115.0±23.2	NS
Profile of mood state (OLS statistics: t: 0.741; df: 46; NS)			
Anger	12.2±4.4	9.4±3.4	0.05
Depression	9.7±2.0	9.5±3.1	NS
Vigor	17.8±3.0	16.9±4.4	NS
Fatigue	10.2±3.6	10.1±5.2	NS
Tension	9.0±3.0	9.1±3.5	NS

Neuropsychological parameter	Controls (n = 25)	FNDI positives (n = 23)	Sign*
Tension caused by the freyuency of social interactions (OLS statistics: t: 0.741; df: 46; NS)			
Negative tension in social interactions	32.0±7.9	29.4±10.6	NS
Incertainty in social interactions	23.0±6.2	22.3±6.3	NS
Positive tension in social interactions	16.3±4.8	15.2±6.7	NS
Frequency of occurrence of negative tension	39.3±9.1	41.3±10.8	NS
Frequency of occurrence of positive tension	21.8±5.0	22.4±6.8	NS
Total score related to tension	94.0±23.5	91.1±31.1	NS
Total score related to frequency	148.6±23.7	152.5±28.7	NS
Questionnaire about memory problems in daily life	60.8±24.7	64.0±27.0	NS
Questionnaire about measures of anxiety	32.6±7.7	31.4±10.2	NS
Decile score of anxiety	3.8±2.5	3.7±2.8	NS
Questionnaire about morning / evening type	23.7±4.0	21.9±3.4	NS

In addition, the requested information was retrieved very slowly. In most cases the information was retrieved after a short while. Other striking findings among the FNDI positive subjects were: switching from subject continuously during a conversation, more sense of humor, more cheerful and showing some kind of indifference in comparison with the FNDI negative subjects.

Although some FNDI negative relatives of the FNDI positive subjects mentioned forgetfulness and/or lack of attention of their FNDI positive relative, no significant difference was found in the memory questionnaire (Baddeley) which measures subjective memory problems in daily life. Significance was even not shown when specific memory questions were analyzed. The FNDI positive subjects were moderately, however not significantly inferior in the performance of an auditory verbal learning test. No marked differences were found except a significant retrieval failure and inferiority in sustained attention in the FNDI positive subjects and they reported less symptoms of agoraphobia and less miscellaneous complaints (see table 1). The inferiority in sustained attention in the FNDI positive subjects suggests that the long-term absence of vasopressin may have a deteriorating effect on certain aspects of attention. The modest differences we found may be caused by the fact that the loss of vasopressin producing neurons seems to be much less in the parvocellular systems which innervate the structures involved in the CNS effects of vasopressin than in the magnocellular neurons which produce the hormone for peripheral antidiuretic effects (4).

FNDI is suggested to be a progressive disease associated with chronic loss of the magnocellular neurons that supply AVP to the posterior pituitary but preservations of the parvocellular neurons. Nothing is known about the state of vasopressin production in other hypothalamic and extrahypothalamic vasopressin neurons and the innervation of brain structures by these neurons in FNDI which are probably mainly responsible for the CNS effects of vasopressin (5). These could well be preserved and thus provide sufficient vasopressin for CNS effects to obscure major cognitive defects. However, there is evidence also about innervation of these structures by magnocellular neurons (10). Some axon collaterals of these neurons may reach some of the extrahypothalamic regions innervated by parvocellular neurons.

Conclusion

Due to the molecular screening of a large family for FNDI positivity, we were able for the first time to perform a neuropsychological study in a relatively homogenous population. Our results indicate moderate, albeit statistically significant differences between neuropsychological measures of the FNDI positive and control subjects, especially in those related to memory retrieval and sustained attention.

References

1. Rittig S, Siggaard C, Ozata M, Yetkin I, Gregersen N, Pedersen EB, Robertson GL. Autosomal dominant neurohypophyseal diabetes insipidus due to substitution of histidine for tyrosine(2) in the vasopressin moiety of the hormone precursor. J Clin Endocrinol Metab 2002; 87: 3351-3355.
2. Mahoney CP, Weinberger E, Bryant C, Ito Mika, Jameson JL, Ito Masafumi. Effects of aging on vasopressin production in a kindred with autosomal dominant neurohypophyseal diabetes insipidus due to the delta E47 neurophysin mutation. J Clin Endocr Metab 2002; 87: 870-876.
3. Nijenhuis M, Akker ELT van den, Zalm, Franken AAM, Abbes AP, Engel H, Wied D de, Burbach JPH. Familial neurohypophyseal diabetes insipidus in a large kindered: effect of the onset of diabetes insipidus on growth in children and cell biological defects of the mutant vasopressin prohormone. J Clin Endocrinol Metab 2001; 86: 3410-3420.
4. De Wied D, Diamant M, Fodor M. Central nervous system effects of the neurohypophyseal hormones and related peptides. Frontiers in Neuroendocrinology, Ganong W.F. and Martini L. (eds) Oxford University Press, London, 1993; 14: 251-302.
5. Kovacs GL, Wied D de. Peptidergic modulation of learning and memory processes. Pharmacol.Rev 1994; 46: 269-291.
6. Bruins J. Desglycinamide-(Arg8)-vasopressin and cognitive processes in healthy subjects, Thesis, University of Utrecht, The Netherlands, 1991.
7. Hijman R, Jolles J, Verhoeven WMH, Ree JM van, Elderson A, Wied D de. Desglycinamide-(Arg8)-vasopressin in five trials with memory-disturbed patients. Human Psychopharm 1992; 7: 7-23.
8. Abbes AP, Bruggeman B, Akker ELT van den. Identification of two distinct mutations at the same nucleotide position, concomitantly with a novel polymorphism in the vasopressin-neurophysin II gene (AVP-NP II) in two Dutch families with familiar neurohypophyseal diabetes insipidus. Clin Chem 2000; 46: 1699-1702.
9. Lezak-Deutsch D. Neuropsychological Assessment (third edition), Oxford University Press, New York, 1995.
10. Hatton GI. Emerging concepts of structure - function dynamics in adult brain: The hypothalamo-neurohypophysial system. Prog Neurobiol 1990; 34: 437-504.