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Skin Vessel Reactivity Is Impaired in Alzheimer's Disease

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ALGOTSSON, A., A. NORDBERG, O. ALMKVIST AND B. WINBLAD. *Skin vessel reactivity is impaired in Alzheimer's disease.* NEUROBIOL AGING 16(4) 577-582, 1995.—Fifteen patients with Alzheimer's disease (AD) and 16 age-matched controls underwent skin vessel reactivity tests employing three vasodilating substances with different modes of action: acetylcholine (ACh), nitroprusside, and isoprenaline. The substances were iontophoresed into the skin and the results were mapped through a newly developed laser Doppler perfusion imager. The skin vascular responses of the patients to ACh and isoprenaline but not nitroprusside were significantly attenuated compared to those of the controls. The differences between patient and control groups concerning skin vessel reactivity might be due to receptor/signal transduction abnormalities but might in addition indicate an attenuated endothelium-dependent vasodilation in AD. The results of this study support the hypothesis that AD might be a systemic disease. They suggest that tests of skin vessel reactivity might be of help in the antemortem diagnosis of AD.

Alzheimer's disease   Skin vessel reactivity   Receptors   Nicotinic   Muscarinic   α- and β-adrenergic
Endothelium-dependent vasodilation   Iontophoresis   Laser Doppler perfusion imager

AMONG other pathologic findings, multiple neuroreceptor changes, signs of impaired signal transduction mechanisms, regional decreases in metabolism and blood flow and amyloid angiopathy have been demonstrated in the central nervous system in Alzheimer's disease (AD) (5,7,23,24). In the early 1980s it was suggested that AD might be a systemic disorder not only confined to the brain (2). Since then, abnormalities concerning membrane function (21), metabolism (28), calcium homeostasis (28), protein kinase activities (27), and signal transduction mechanisms (15,24) have been reported in peripheral, nonneural tissues in patients with AD. In peripheral lymphocytes losses of muscarinic and nicotinic receptors have been found (1,25). A correlation between the degree of dementia and the number of nicotinic receptors in lymphocytes of AD patients has also been reported (24). These studies of peripheral tissues mostly blood cells and skin fibroblasts were done in the search for antemortem markers of the disease. Signs of autonomic dysfunction in AD have also been demonstrated (4,10,12).

To our knowledge, only one previous study concerning skin vessel reactivity in AD is available (17). We wanted to study skin vessel reactivity in AD to three vasodilating substances with different modes of action—acetylcholine (ACh), nitroprusside, and isoprenaline.

METHOD

The method used in this study for tests of skin vessel reactivity has been described and evaluated previously (3).

Exclusion Criteria

Smoking or the use of smokeless tobacco, medication of any kind, history, symptoms or signs of cardiovascular disease, diabetes, coloured skin, atopic constitution, generalized dermatitis, psychiatric illness, devastating disease of any kind other than dementia in the patient group and, for the controls, brain disease and a Mini Mental State Examination (MMSE) (11) score less than 28/30, precluded participation in the study.

Subjects

Fifteen patients (5 men; 10 women, mean age = 70.0 years ± 8.3, range = 57-82) were examined. Eleven fulfilled the diagnostic criteria of probable AD and 4 of possible AD according to the criteria of NINCDS-ADRDA (22). The patients entered the study over a period of 11 months. They were subjected to the following investigations to establish the diagnosis of AD, to exclude other disorders causing dementia, and to rule out the

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exclusion criteria: Recording of family and medical history, neuropsychological testing, routine blood tests (including electrolyte panel, glucose and albumin tests, thyroid function tests, serum cobolamin and folate levels), urine analysis, cerebrospinal fluid (CSF) tests (protein, glucose, and cell count), blood and CSF tests for syphilis, Borreliosis and HIV, electrocardiogram, chest X-ray, electroencephalography, computerized tomography (CT) scan, and/or magnetic resonance imaging (MRI) of the brain.

If possible, the tests were performed early in the disease process. Three patients did not fulfill all the criteria of dementia when the skin vessel reactivity tests took place but subsequent follow-up established the diagnosis. All patients were in good general health and lived in their own homes, in some cases with assistance from relatives and/or home service personnel. One man had a history of Raynaud's syndrome earlier in life when he worked with vibrating tools but no symptoms or signs of vascular disease when examined. We found no reason to exclude the patient from an investigation of this kind (9).

Sixteen healthy subjects (5 men; 11 women, mean age = 70.2 years ± 7.5, range = 54–82) living in their own homes and caring for themselves served as controls. According to their medical history all subjects ruled out the exclusion criteria mentioned above and no subject had a family history of dementia disorders; 4 subjects belonged to the hospital staff, working full time; 6 subjects were identified from a population study and 6 were volunteers from a pensioners association. Those 12 subjects and the oldest subject belonging to the hospital staff underwent the following tests to confirm that they fulfilled the exclusion criteria: physical examination, electrocardiogram, and the same routine blood tests and urine analysis as the patients. For further details about patients and controls, see Table 1.

All patients and/or their next of kin and all controls gave their informed consent and the study was accepted by the Ethical committee of Huddinge University Hospital.

Iontophoresis and Laser Doppler Perfusion Imaging

Iontophoresis noninvasively enhances the penetration of charged substances into the skin with the aid of an electric current. The iontophoretic equipment used is a modified copy of one previously described (18). The anode is a multi-electrode device with 11 chambers, the current to each of the chambers can be varied or totally switched off when necessary. The rise in tissue perfusion caused by iontophoresis of the vasoactive drugs was mapped with a newly developed laser Doppler perfusion imager (35). A computer-controlled optical scanner moves the laser beam step-by-step in a rectangular pattern over the skin surface. A fraction of the light is Doppler-shifted by the moving blood cells and converted into an electrical signal which relates linearly to tissue perfusion. The output signal of the processor is sampled and stored by a personal computer and a color coded image is generated. Further image processing and data analysis are made in the displayed image. We made some alterations in the data program provided by the inventors, enabling us to pin point the measurement sites we wanted to analyse. It is possible to present the result on a colour plotter.

Drugs

ACh chloride, sodium nitroprusside, and isoprenaline sulphate were the vasoactive drugs used. They were stored as dry matter and were dissolved in distilled water immediately prior to the experiments. ACh in the form of dry matter was stored

TABLE 1
SOME PATIENT AND CONTROL CHARACTERISTICS

	Patients	Controls
Number	15	16 (15)*
Age (years) (range)	70.0 ± 8.3 (57–82)	70.2 ± 7.5 (54–82)
Men/women	5/10	5/11 (5/10)*
Systolic blood pressure (mm Hg)	131 ± 18	127 ± 19
Diastolic blood pressure (mm Hg)	73 ± 9	75 ± 6
Total cholesterol (mmol/l)	6.4 ± 1.4	6.5 ± 1.1
Positive family history of dementia	8/14†	0/16
MMSE (range)	18.8 ± 6.5 (6–28)	≥28
Age at onset of symptoms (range)	65.9 ± 7.6 (53–78)	—
Duration of the disease (range)	4.1 ± 2.7 (1–12)	—

*One of the controls was not tested with nitroprusside; †Data missing for 1 patient. Mean ± SD.

in a freezer (-18°C). The drugs were provided by the pharmacy of the Huddinge University Hospital.

Experimental Procedure

Measurements were made after 20–30 min acclimatisation in a warm room (25.8 ± 0.9°C) to reduce sympathetic vasoconstrictor tone. The subject rested comfortably in supine position under blankets with one arm outstretched, the forearm positioned at heart level. The pulse and blood pressure were tested at the beginning and the end of the procedure and the skin temperature was monitored throughout the experiment, thermistor probes being attached to the arm just distal to the antecubital fossa and to the tip of the third finger. The anode was placed over grossly normal skin on the flexor aspect of the forearm and secured with two adjustable straps. The cathode, a brass metal plate, was covered with a pad moistened with 0.9% NaCl solution and attached on the same arm opposite to the anode. Three chambers were used and filled with the following solutions: ACh chloride, 1.1 mM, sodium nitroprusside, 0.67 mM, and isoprenaline sulphate, 0.18 mM. In spite of the differences in molarity the effects of the three drugs were similar.

The current used during iontophoresis of drugs is reported to be of more importance for the effect of the drugs than the molarity (18). The current was set to 220 μA for 30 s. Initially the poles were set for iontophoresis of the negatively charged nitroprusside, then they were switched for iontophoresis of the two other substances. In connection with the iontophoresis the sites of reaction to the three drugs were marked on the skin. The tissue perfusion was mapped 4 and 10 min after the start of the iontophoresis. The scanning procedure took about 1 and 1/2 min for a skin area of about 3 × 8 cm corresponding to ~1550 measurement sites.