Letters

Reduction in muscarinic receptor binding in limbic areas of Alzheimer brain

Sir: It has been shown in many studies that there is a marked loss of presynaptic cholinergic neurons in patients with Alzheimer’s disease.1,2 Prominent histological changes are seen in the limbic structures, especially the amygdala and hippocampus.3,4 It has also been shown that the neuronal loss in the hippocampus of patients with Alzheimer’s disease is five times greater than in normal ageing.5 Recent studies have shown that isodendritic neurons which project from the nucleus basalis of Meynert to the cerebral cortex and from the diagonal band of Broca and the medial septal nucleus to hippocampus are especially affected.6-8 It is not clear whether there are changes in the muscarinic receptors in patients with Alzheimer’s disease since the results published so far are contradictory. Muscarinic receptor binding has mostly been reported to be normal.5-11 On the other hand, Reisine et al12 found that muscarinic receptor binding was decreased in the hippocampus of patients with Alzheimer’s disease. In order to clarify this matter we have recently studied changes in brain muscarinic receptors in Alzheimer’s disease demonstrating limbic impairment.

Twenty-five brains of patients with Alzheimer’s disease (mean age 79 ± 1 years) and 31 from control subjects (mean age 76 ± 2 years) were examined. The diagnosis of Alzheimer’s disease was neuropathologically verified and it was checked that the age-matched control patients showed no evidence of neurological disease. Sixteen of the Alzheimer’s disease patients were treated with neuroleptic drugs and none received anticholinergic treatment. Muscarinic receptors were studied by the specific binding of 3H-QNB ([3H]-quinuclidinyl benzilate, Amersham), by the method of Reisine et al.13 Tissue concentration used was 2 mg/assay (0-1 mg protein/assay). The concentration of 3H-QNB used for the single estimations was 80 pM and the range of concentrations used for the Scatchard analysis was 5-200 pM.

As can be seen from the table, muscarinic receptor binding was decreased in the hippocampus, amygdala and nucleus accumbens in patients with Alzheimer’s disease. According to Scatchard analyses from hippocampus samples the decreased binding of 3H-QNB was due to a decrease in the number of receptors (Bmax (fmol/ mg prot.) 473 ± 21.1 for controls and 352 ± 28.0 for Alzheimer’s disease, p < 0.01) but there was no significant change in the mean dissociation constant (Kd (pM) 19.3 ± 0.6 for controls and 20.8 ± 0.9 for Alzheimer’s disease). Treatment with neuroleptic drugs had no effect on muscarinic receptor binding in Alzheimer’s disease patients (Table).

These findings show that cholinergic neurons in the limbic system are especially vulnerable in Alzheimer’s disease. It is possible that the decrease in the number of muscarinic receptors is due to the severe impairment of the cholinergic neurons in the limbic system, whereas the cholinergic system in the neocortex is not so severely affected, and therefore muscarinic receptor binding is not significantly altered. On the other hand, the decrease in muscarinic receptor binding in limbic system may be related to severe postsynaptic cell loss in these areas of the Alzheimer’s disease brain. We have previously shown that treatment with neuroleptic drugs increases 3H-QNB binding.14 In the present material, however, this did not take place, perhaps because of the severely damaged brain cholinergic system in Alzheimer’s disease. Our results give support to the previous observation of the substantial role of the limbic system in Alzheimer’s disease suggested by the fact that the hippocampus and other limbic regions are most important for learning, memory processing and memory recall, all of which are typically impaired in Alzheimer’s disease patients.15,16

Table. Muscarinic receptors examined by 3H-QNB binding (fmol/mg prot.) in brains of controls and patients with Alzheimer’s disease. Mean ± S.E.M.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>3H-QNB binding</th>
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<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>All cases</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>1083 ± 41.8</td>
</tr>
<tr>
<td>Putamen</td>
<td>1047 ± 39.4</td>
</tr>
<tr>
<td>Pallidum</td>
<td>19 ± 12.6</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>696 ± 29.3</td>
</tr>
<tr>
<td>Accumbens</td>
<td>812 ± 59.0</td>
</tr>
<tr>
<td>Amygdala</td>
<td>539 ± 19.2</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>398 ± 16.4</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01, ††p < 0.001 compared with control

Number of patients in brackets

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Metastatic carcinoid tumour compressing the cauda equina

Sir: We report a patient with a progressive syndrome of cauda equina compression due to an osteogenic metastasis from an intestinal carcinoid tumour.

A 64-year-old female presented with a one year history of low back pain irradiating to both legs for three months. Prolonged sitting caused numbness in both thighs. Six months before she had been examined for these complaints at another hospital, and radiographs of the lumbar spine were reported normal. She had a ten year history of abdominal pain and intermittent diarrhoea and two years previously had presented with acute intestinal obstruction. A small bowel carcinoid was removed at operation. There were multiple metastases to the mesentry and abdomino-lumbar lymph nodes. Physical examination showed bilateral grade 4 quadriceps weakness; the knee and ankle jerks on the right side were reduced. Straight leg raising was normal on both sides but there was bilateral femoral nerve stretch pain. Cauda equina compression at the L3 level was presumed. Plain radiographs of the lumbar spine showed sclerosis of the body and the right pedicle of L3. Metrizamide myelography demonstrated a complete block at L3. CSF analysis including a smear of the sediment was unremarkable. At surgery a highly vascular tumour was found in the epidural space opposite L3. The tumour was carefully debulked and no cauda equina compression could be attributed to the tumour. The lumbar spine was irradiated with 6000 rads. Signs and symptoms disappeared and the patient remained well for 12 months. Postoperatively she complained of periods of flushing which reacted well to methysergide. She died 15 months later following multiple abdominal complications included intestinal obstructions.

Although carcinoid tumours were initially considered as non-infiltrating and non-metastasing, subsequent case reports illustrated that carcinoid tumours may metastasise to the lymph nodes and very rarely to the nervous system. To our knowledge only one well-documented case of cervical spinal cord compression has been published and no case of cauda equina compression has been reported. When our patient presented with low back pain and inconstant radicular symptoms, the presence of degenerative bone disease or disc pathology was much more probable than metastatic carcinoid tumour. Plain radiographs of the spine six months previously were normal but at a later stage there were discrete abnormalities on plain radiographs of the lumbar spine. As osteoblastic metastases are well recognised complications of malignant carcinoid tumours, further examinations were performed and showed a metastasis at L3. This seems a very rare complication of carcinoid tumour. A neurofibroma had also to be excluded, because the combination of carcinoid and von Recklinghausen’s neurofibromatosis had been stressed in two previous reports.

In conclusion, the patient illustrates that in presence of persisting spinal pain, radiculopathy or myelopathy, a vertebral metastasis should be considered even when the primary tumour is of carcinoid origin. As in the case of other bone metastases a bone isotope scan has to be performed even when plain films of the spine are normal while also an immuno-assay technique with specific antibodies to serotonin may be a very sensitive method of carcinoid metastasis detection. These procedures may detect the lesion earlier, resulting in temporary pain relief by röntgen irradiation. Our patient remained pain free for one year.

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