Neuropathology and Applied Neurobiology (2001), **27**, 1–4

Annotation
Hippocampal plasticity in children with epilepsy

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W. Squier and S. Sisodiya (2001) *Neuropathology and Applied Neurobiology* **27**, 1–4
Hippocampal plasticity in children with epilepsy

Three main types of pathological change are recognized in the hippocampus in children with epilepsy: neuronal loss and gliosis, mossy fibre sprouting and dentate dispersion. In mesial temporal sclerosis (MTS) there is increasing evidence that cell loss in specific subfields of the hippocampus may be related to age at precipitating injury. The relationship of febrile or complicated seizures to MTS remains unclear. Mossy fibre sprouting is a manifestation of reorganization and plasticity of the neuronal processes of the dentate granule cells but the stimulus for mossy fibre sprouting remains unclear despite insights from both experimental work and studies in human epilepsy. Two main patterns of structural changes in the dentate gyrus have been described in human epilepsy: generalized dispersion with granule cell bodies identified in the molecular layer or separation of the dentate gyrus into two distinct laminae. There appears to be no consensus on the criteria for defining dentate dispersion. There is continuing controversy over the influence of seizure type and history on hippocampal damage. It is increasingly recognized that the brain is capable of continuing plasticity for many years after birth. In the hippocampus this leads to multiple patterns of pathology. While these processes have been considered damaging and a cause of further epilepsy they may also represent adaptive change, with beneficial effects on other functions such as memory or they may in fact inhibit seizure activity.

Keywords: epilepsy, childhood, mesial temporal sclerosis, pathology

Introduction

During the last 10 years we have gained many new insights into processes of neuronal plasticity and in particular into changes which occur in the hippocampus in children with severe epilepsy. Three main types of pathological change are recognized in the epileptic hippocampus, neuronal loss and gliosis, mossy fibre sprouting and dentate dispersion.

Neuronal loss

Severe neuronal loss, particularly from CA1, CA3 and CA4 regions of Ammon's horn and from the dentate gyrus has been recognized for many years as mesial temporal sclerosis (MTS). Cell loss from the dentate gyrus is more marked in children where seizures began before four years of age [25]. Cell loss from the subgranular or polymorphic region of the hippocampal hilus was noted by Houser [9].

There is increasing evidence that cell loss in specific subfields of the hippocampus may be related to age at precipitating injury. MTS has been associated with febrile seizures in childhood but not with birth-associated injury [13,15] while the degree of cell loss is influenced by the age of initial precipitating injury [13]. In a group of patients with intractable epilepsy associated with remote middle cerebral artery infarction there was a clear distinction between those whose infarct had occurred in the first years of postnatal life and those with prenatal stroke [28]. Those with postnatal infarction showed severe MTS

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which was not seen in the children with intrauterine damage although both groups had subgranular hilar gliosis and mossy fibre sprouting.

Mossy fibre sprouting

Mossy fibre sprouting is a manifestation of reorganization and plasticity of the neuronal processes of the dentate granule cells which has been identified, in both human epileptic temporal lobes and in animal models [8,9]. Newly formed axonal processes, originating in dentate granule cells, grow through the dentate gyrus and into the overlying molecular layer producing a dense network of processes, usually identified by staining with Timm's method or dynorphin immunocytochemistry [2,9]. Antibodies to the microtubule-associated protein, MAP-2, demonstrate intense staining of granule cell dendrites extending into the supragranular molecular layer. This change has been shown in children studied with epilepsy but not in age-matched controls and occurs irrespective of the presence of MTS (29). This upregulation of microtubule protein expression in dentate cell dendrites may be a response to their innervation by sprouted mossy fibres. Alterations in the morphology of dendritic spines in response to novel innervation on these dendrites has been demonstrated [23], and MAP-2 is known to be expressed contemporaneously with synaptogenesis [11,26].

The growth-associated protein, GAP-43, is transiently expressed in early mossy fibre sprouting [3] and is also upregulated in the supragranular molecular layer of children with chronic epilepsy.

Continuing neuronal plasticity in adults is suggested by demonstration of an increase in polysialylated neural cell adhesion molecule (PSA-NCAM) in the dentate molecular layer in patients with epilepsy [17]. Indeed experimental studies in adult primates show progressive sprouting with increased survival time after induction of seizures [24].

Golgi studies and electron microscopy indicate that the cause of seizures may influence patterns of sprouting. Rats with kindled seizures but without neuronal loss developed sprouting but it was less complex and extensive than in rats with kainate-induced seizures and Ammon's horn sclerosis [23].

The stimulus for mossy fibre sprouting remains unclear. An association with loss of hilar neurones was demonstrated some years ago [1] and led to the hypothesis that mossy fibre sprouting was a simple consequence of hippocampal neurone loss. However subsequent studies have shown no correlation between density of mossy fibre sprouting and hilar neurone loss [13] indicating that mossy fibre sprouting may be induced by other mechanisms.

The consequences of these reorganized networks and their influence on subsequent epileptogenesis remain uncertain. There are electrophysiological indications of increased and abnormal excitability [20] but an inhibitory effect is also recognized [9]. These changes may thus be adaptive and beneficial. Inhibition of mossy fibre sprouting in rats with induced seizures does not prevent continued seizure activity [16].

It has been suggested that seizures induce granule cell proliferation in the adult rat hippocampus [21], and that newly sprouted mossy fibre axons arise from recently generated cells. However, complete inhibition of neurogenesis by brain irradiation does not inhibit mossy fibre sprouting in rats, indicating that sprouting does not depend on generation of new cells [22]. The well-recognized reduction of cell numbers in the dentate gyrus in patients with chronic epilepsy is evidence against seizure-induced neurogenesis.

Dentate dispersion

Structural changes in the dentate gyrus were first described in human epilepsy by Houser in 1990 [8]. Two main patterns were described, generalized dispersion with granule cell bodies identified in the molecular layer or separation of the dentate gyrus into two distinct laminae [9].

There appears to be no consensus on the criteria for defining dentate dispersion. Morphometric assessments of dentate gyrus width or granule cell density have been used [9,10]. As the dentate gyrus undergoes considerable change in size and cell density with age and the pathology varies in anterior–posterior extent [9,20], morphometric studies must be accompanied by the use of carefully selected age and position-matched controls.

It was suggested that dispersion resulted from damage during development causing altered cell proliferation or migration, possibly continuing in the first years of postnatal life. In the human brain expression of an immature form of neural cell adhesion molecule (NCAM-H) in the first years of life has been used as evidence for continued migration [12]. Evidence for continued granule cell

proliferation is less secure. Bromodeoxyuridine (BrDU) incorporation into the granule cells of adult dentate gyrus [6] is evidence of re-entry of the cells into the cell division cycle and replication of DNA. This may be a non-specific response to injury which precedes neuronal death [18]. Mitosis has not been demonstrated.

Granule cell dispersion has been linked to epileptic events in the first 4 years of life but not with duration or number of seizures [10]. Interruption of migration might be expected to result in heterotopic neurones in the migration pathway beneath the granule cell layer: such heterotopic neurones are not commonly seen. Dispersion of dentate granule cells has however, been experimentally induced in adult rats [21] and monkeys where associated gliosis and capillary proliferation were considered evidence for acquired damage [24].

Clinical correlations and relevance of seizure history

There is continuing controversy over the influence of seizure type and history on hippocampal damage. The relationship of febrile or complicated seizures to MTS remains unclear [27]. Only a minority of children studied by magnetic resonance imaging (MRI) after febrile convulsions showed acute changes leading to hippocampal atrophy while a greater proportion had evidence of hippocampal atrophy predating the febrile seizures [29].

MRI volumetric studies have shown no correlation between hippocampal atrophy and age, length of history or frequency of seizures [4,7]. Progressive hippocampal atrophy has been documented in a single patient with non-status seizures [19]. The drawback with MRI volumetric studies is that they show overall loss of volume but do not distinguish the specific underlying patterns of cell loss further; to date there have been no large scale longitudinal studies. All hippocampal atrophy may not necessarily be MTS.

Histological studies have shown a correlation between severity of hippocampal cell loss and duration of epilepsy and frequency of seizures [5,14].

Conclusion

It is increasingly recognized that the brain is capable of continuing plasticity for many years after birth. In the hippocampus this leads to multiple patterns of pathology. While these processes have been considered damaging and a cause of further epilepsy they may also represent adaptive change, with beneficial effects on other functions such as memory or they may in fact inhibit seizure activity.

Surgical treatment of intractable epilepsy continues to provide resected tissue for study. This is a precious resource and its value must be recognized. Careful preservation of this material and development of collaborative research efforts will further our understanding of human epilepsy.

Acknowledgements

The authors would like to thank Professor Margaret Esiri for helpful discussions and Samantha Cragg for help in preparing the manuscript. The authors were supported by funding from the Epilepsy Research Foundation and *Neuropathology and Applied Neurobiology*.

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Received 8 May 2000
Accepted after revision 8 June 2000