John was always on the look out for new possible autoimmune disorders, and the Lambert Eaton myasthenic syndrome was a good candidate. He found that plasma exchange was effectively in these patients too, and Bethan Lang with Dennis Wray demonstrated that there were antibodies against the voltage-gated calcium channels on the presynaptic motor nerve terminals and that the associated small cell lung cancers expressed this antigen. The final autoimmune disease of the NMJ was not discovered until the 1990s when similar experiments, partly by Ian Hart, showed that acquired neuromyotonia was associated with antibodies to the presynaptic voltage-gated potassium channel. In all of these studies the importance of having specific neurotoxins that bind to the receptors and ion channels at the NMJ cannot be overstated. The lecture will try to give a historical perspective and update the audience on these conditions.

Friday, 26th March 2010

O08 Oral presentation

Reactive oxygen species and loss of muscle fibres during ageing

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Reactive oxygen species (ROS) appear to play a role in the fundamental processes underlying ageing and studies have examined the potential role of these species in the loss of muscle fibres that occurs during ageing. Skeletal muscle of young or adult animals has a remarkable capacity to adapt to an increase in the generation of ROS that occurs during physiological processes by up-regulation of a variety of regulatory proteins for ROS. During ageing these adaptive processes become ineffective and muscles of aged rodents shows no increase in the muscle content of antioxidant enzymes or heat shock proteins following contractile activity in comparison with that seen by muscle from adult or young rodents. In addition, ROS generation appears to increase with ageing since isolated mitochondria from muscle of ageing rodents show an increased release of hydrogen peroxide in comparison with mitochondria isolated from young rodents. Together these data suggest that restoration of the ability of muscle from aged organisms to respond to ROS might influence age-related loss of muscle mass and function. This possibility has been examined by genetic overexpression of heat shock proteins in muscle of mice. This manipulation has been found to prevent the age-related loss of muscle force production seen in aged mice indicating potential therapeutic approaches that may reduce loss of muscle mass and function in elderly human subjects.

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O09 Oral presentation

Inclusion body myositis – an age related degenerative myopathy?

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Inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy occurring in patients over age 50. Muscle biopsy characteristically reveals endomysial inflammation, small groups of atrophic fibers, eosinophilic cytoplasmic inclusions, and muscle fibers with one or more rimmed vacuoles. However, any given biopsy may lack these histopathological abnormalities so the key to diagnosis is the pattern of involvement of muscle groups on clinical examination. Early and often asymmetrical weakness and atrophy of the quadriceps and flexor forearm muscles (i.e., wrist and finger flexors) are the clinical hallmarks of IBM. The pathogenesis of IBM is unknown. It may be autoimmune inflammatory myopathy or a primary degenerative myopathy with a secondary inflammatory. Some investigators purport that proteins that accumulate in brains of patients with Alzheimer disease are evident by immunohistochemstry in IBM muscle. This has led to the theory that β-APP is overproduced in IBM muscle fibers, that this is somehow cleaved into abnormal β-amyloid, and the accumulation of the later or "tau" is somehow toxic to muscle fibers. However, there are problems with this theory. Unfortunately, IBM is generally refractory to therapy. Further research into the pathogenesis, along with both preliminary small pilot trials and larger double-blind, placebo-controlled efficacy trials are needed to make progress in our understanding and therapeutic approach for this disorder.

O10 Oral presentation

Protein aggregate myopathies and ageing

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While many forms of inherited muscle disorders primarily affect children, hereditary inclusion body myopathies (hIBM) and myofibrillar myopathies (MFMs) are almost exclusively seen in adults. Depending on the exact genetic defect, first symptoms start between the 3rd and the 7th decade, suggesting a role of ageing in the pathomechanism. The 2 most frequently found forms of inherited IBM in the UK are caused by mutations in GNE and in VCP. GNE mutations are associated with the recessive form of hIBM, characterized clinically by foot drop and sparing of the quadriceps muscle. VCP mutations cause an autosomal dominant form of IBM that is often associated with Paget's Disease and with FrontoTemporal Dementia (IBMPFD). Myofibrillar myopathies (MFM) are characterized by specific morphological changes and caused by mutations in several genes (such as the desmin and the myotilin-encoding genes), most of them Z-disc related. In addition, MFM frequently present rimmed vacuols. Protein aggregates are frequently observed in these disorders reminiscent of protein aggregates in age-related disorders of the brain.

O11 Oral presentation

New findings in FSHD

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The genetic lesion in >95% of patients with FSHD, a loss of an integral number of subtelomeric D4Z4 repeats (<11 repeats) on chromosome 4qter, was first described in 1993. Yet, until recently, the underlying molecular mechanism remained an enigma. The D4Z4 repeats, contains an open reading frame, *DUX4*, for which, it has been difficult to demonstrate a stable transcript or protein in somatic cells. An alternative hypothesis was that loss of a critical number of repeats, a buffer between heterochromatic and euchromatic DNA, led to dysregulation of genes centromeric to the repeats. However, no consistent, reproducible change in centromeric gene expression was found. Several lines of evidence now point back to *DUX4*. The *DUX4* gene is evolutionarily conserved and several *DUX4* transcripts and proteins are produced by the D4Z4 repeat. In addition, pathogenic contraction of the D4Z4 repeats occurs on a distinct 4qter haplotype (4qA161) and is associated with a permissive change in chromatin structure limited to the repeat array. Supporting a pathogenic role for the chromatin changes is the occurrence of D4Z4-restricted hypomethylation in a subpopulation of FSHD (FSHD2), in whom no contraction in the number of D4Z4 repeats occurs. The current prevailing hypothesis for the molecular mechanism of FSHD postulates that the permissive chromatin changes at D4Z4, whether or not associated with loss of a critical number of repeats, results in perturbation in the basal expression of *DUX4*. The *DUX4* a pro-apototic protein, can interfere with normal myogenesis and make cells more susceptible to oxidative stress.