Evaluation of the molecular basis of pathogenicity of the variant Newcastle disease viruses termed “pigeon PMV-1 viruses”

Brief Report

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Summary. The amino acid sequence at the F2/F1 cleavage site was determined for 15 strains of the so-called pigeon PMV-1 (PPMV-1) variant of Newcastle disease virus (NDV) which showed close antigenic identity, determined by their reactions with a panel of 28 monoclonal antibodies, but considerable variation in their pathogenicity for chickens. Thirteen of the isolates possessed the motif 112G-R-Q-K-R-F117. This motif was seen for one virus which had initially low pathogenicity and remained unaltered when virulence of the virus for chickens was increased by bird to bird passage. The two other viruses had the sequence 112R-R-Q-K-R-F117 at the cleavage site which is more typical of virulent viruses, however, pathogenicity index tests indicated that these isolates were of moderate and low pathogenicity. The nucleotide sequence coding for the HN/HN0 extension region was determined for two of the PPMV-1 isolates. In both cases a stop codon was present indicating that the product for these viruses would be HN571. We conclude that the wide variation in pathogenicity of the variant PPMV-1 for chickens is not related to variation in the amino acid motif at the F2/F1 cleavage site nor due to production of HN0 which may also influence pathogenicity. The high virulence of some of the viruses examined confirms that a double pair of basic amino acids in the region of the F2/F1 cleavage site is not necessary for the full expression of virulence.

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During 1981 to 1985 infections of racing and show pigeons with an avian paramyxovirus type 1 (APMV-1) virus became world-wide [17]. Use of a panel of monoclonal antibodies confirmed the variant nature of the virus responsible when compared to more classical Newcastle disease (ND) viruses [4], and also the antigenic similarity of isolates of the virus affecting pigeons [2].
Assessment of the pathogenicity of viruses identified as the pigeon variant APMV-1 (PPMV-1) for chickens has shown some ambiguity. Many isolates examined have had values obtained in intracerebral pathogenicity index (ICPI) tests in day-old chicks of around 1.4 and low or zero values in intravenous pathogenicity index (IVPI) tests in six-week-old chickens [2]. However, Alexander and Parsons [1] demonstrated that after passage through chickens IVPI values of > 2 and increased ICPI values could be obtained with some isolates. This is in keeping with the finding that most of the isolates of the PPMV-1 virus affecting chickens in the 1984 outbreaks in Great Britain had very high pathogenicity indices [3].

In recent years a much greater understanding of the molecular basis of the pathogenicity of ND viruses has come about as a result of the work of Rott, Klenk and co-workers [14]. In the replication of ND virus the virus particles produced are only infectious if a post-translational cleavage event mediated by host proteases has occurred which results in the production of two proteins F1 and F2 from the precursor fusion protein, F0. ND viruses which are virulent for chickens appear to have an F0 protein which can be cleaved by a ubiquitous host protease(s) found in most tissues, and may thus produce a systemic infection and ultimately fatal disease. In contrast, the F0 proteins of viruses of low virulence for chickens require trypsin-like enzymes to bring about cleavage and these viruses appear, therefore, to be restricted to growth in the respiratory and intestinal tracts. The cleavability of the F0 protein appears to be mediated by the amino acids at the cleavage site. In a recent report Collins et al [6] concluded that of 26 PMV-I (NDV) isolates sequenced at the cleavage site all 14 viruses that were pathogenic for chickens had the sequence 112R/K-R-Q-K/R-R\text{116} at the C-terminus of the F2 protein and F (phenylalanine) at residue 117, the N-terminus of the F1 protein; whereas the 11 viruses of low virulence had sequences in the same region of 112G/E-K/R-Q-G/E-R\text{116} and L (leucine) at residue 117. Thus there appeared to be the requirement of a double pair of basic amino acids at residues 112 and 113 and 115 and 116 plus a phenylalanine at residue 117 if the virus was to show virulence for chickens. The exception was the single pigeon variant virus that was examined which had the sequence 112G-R-Q-K-R-F\text{117}, this virus had pathogenicity indices typical of PPMV-1 isolates, ICPI 1.47 and IVPI 0.00. Jestin and Cherbonnel [9] have shown a similar motif at the F2/F1 cleavage site for two viruses isolated from chickens which they group antigenically with PPMV-1 viruses [10].

Nucleotide sequences of the HN gene of different ND viruses has indicated that the HN protein may be produced in three different sizes of 571, 577 or 616 amino acids depending on the position of termination codons in the gene [15]. The largest form, HN0{\text{616}}, requires proteolytic cleavage for conversion to the biologically active form [12], but the two others, HN{\text{577}} and HN{\text{571}}, appear to be already biologically active. Because the HN protein is involved in receptor binding and possesses neuraminidase activity, the production of the biologically inactive HN0 could influence pathogenicity. To date all viruses shown to code for HN0 have been the viruses of extremely low virulence for