Reverse phylogenetic approach to discovery of novel adrenomedullins in mammals

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In this paper, we introduce how the use of comparative studies leads to the discovery of novel adrenomedullins (AMs) in mammals. The calcitonin gene-related peptide (CGRP) family in mammals was thought to consist of CGRP, AM and amylin. By comparative genomic analyses, we found five AMs (AM1~5) in teleost fish, of which mammalian AM is an ortholog of teleost AM1. We showed that AM1, AM2, and AM5 existed before the divergence of teleosts and mammals. Based on these results, we searched for the AM2 and AM5 genes in the genome databases of mammals and identified both genes in several species. AM2 was shown to be a circulating hormone in the blood of humans, but the human AM5 gene has a two-base deletion in the coding region. The deletion must have occurred just before the appearance of the gorilla because no such deletion was observed in the orangutan AM5 gene and this species produces AM5. In addition, we used comparative studies to suggest the presence of a novel receptor for AM2 and AM5 that differs from the AM receptor thus far known in mammals and teleosts. Previously, novel hormones and their receptors have been discovered first in mammals and then later in fishes. Since our approach (from fishes to mammals) is in the opposite direction from the orthodox approach (from mammals to fishes), we have named it the 'reverse' phylogenetic approach to emphasize the merit of comparative studies.