

## Existence of multiple receptors for neurohypophysial hormones in cartilaginous fish.

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Neurohypophysial hormones (vasopressin- and oxytocin-family peptides) are crucial in the maintenance of vertebrate homeostasis and reproduction. To date, three types of vasopressin-family receptors (V1a, V1b and V2) and one type of oxytocin-family receptor have been identified and extensively studied in tetrapods. However, the work on these receptors in fish lags behind that in other vertebrates.

In this study, we successfully cloned four putative neurohypophysial hormone receptors from the cartilaginous elephant fish, *Callorhynchus milii* (Holocephali). Molecular phylogenetic analysis suggests that the four elephant fish (ef) receptors are grouped into the V1a, V1b, V2 and oxytocin receptor families, respectively. In functional analysis using CHO cells transfected with the cloned cDNAs, putative efV1 receptors stimulated intracellular  $\text{Ca}^{2+}$  accumulation in response to vasotocin, as has been observed in other vertebrates. Surprisingly, vasotocin-stimulated activation of a putative efV2 receptor also caused the accumulation of  $\text{Ca}^{2+}$  rather than cAMP. Further analysis of teleost fish receptors revealed that a new fish-specific receptor subfamily, the V2-like receptor; efV2 receptor is included in this subfamily. A putative elephant fish oxytocin receptor was not specifically selective for oxytocin, but showed high affinity to both oxytocin and vasopressin family peptides. The evolutionary history of the neurohypophysial hormone system will be discussed.