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Current Opinion in Neurobiology

Reconciling the deep homology of neuromodulation with the evolution of behavior

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The evolution of behavior seems inconsistent with the deep homology of neuromodulatory signaling. G protein coupled receptors (GPCRs) evolved slowly from a common ancestor through a process involving gene duplication, neofunctionalization, and loss. Neuropeptides co-evolved with their receptors and exhibit many conserved functions. Furthermore, brain areas are highly conserved with suggestions of deep anatomical homology between arthropods and vertebrates. Yet, behavior evolved more rapidly; even members of the same genus or species can differ in heritable behavior. The solution to the paradox involves changes in the compartmentalization, or subfunctionalization, of neuromodulation; neurons shift their expression of GPCRs and the content of monoamines and neuropeptides. Furthermore, parallel evolution of neuromodulatory signaling systems suggests a route for repeated evolution of similar behaviors.

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Current Opinion in Neurobiology 2014, **29**:39–47

This review comes from a themed issue on **Neuromodulation**

Edited by **David A McCormick** and **Michael P Nusbaum**

For a complete overview see the Issue and the Editorial

Available online 27th May 2014

http://dx.doi.org/10.1016/j.conb.2014.05.002

Introduction

There is remarkable deep homology [1,2] of the molecules used for neural signaling that goes back to the earliest metazoans, before there were nervous systems. Yet, extant animals display a great diversity of behavior; even closely related species can differ in heritable behavior. The apparent contradiction of slow, conservative evolution of the nervous system, but rapid behavioral evolution is central to understanding of how behavior evolves. Namely, it is less about the invention of new molecules and more about their modification and compartmentalization. Neuromodulation, which plays a role in behavioral plasticity, relies on G protein coupled receptors (GPCRs) and their ligands, including neuropeptides and monoamines. Although these receptors and ligands are ancient, we suggest that differences in their compartmentalization played a dominant role in the evolution of behavior.

The dynamics and activity patterns of neural circuits are constrained by the membrane properties of the component neurons and by the strengths of the synapses between them, both of which can be modulated by neuropeptides and monoamines (see this issue: Nadim and Bucher; Komuniecki *et al.*). In this way, neural circuits can be multifunctional, producing different outputs under different neuromodulatory conditions [3–6] (see also this issue: Cropper *et al.*; el Manira *et al.*). Just as neuromodulation causes a neural circuit in an individual animal to produce multiple outputs or process information differently, so too can species-differences in neuromodulation cause different ranges of behavior. As we will discuss, the cellular localization of receptors and neuromodulatory substances varies across species in ways that correlate with behavior.

Evolution of neuromodulatory signaling through gene duplication, neofunctionalization, and loss

The molecular components of neural signaling first appeared before there were nervous systems. GPCRs, the cell surface receptors upon which peptides and monoamines commonly act, arose early in metazoan evolution [7]. They subsequently diverged through a series of gene duplication events [8–10]. Following duplication, unnecessary or redundant genes generally undergo negative selection. However, GPCRs have been preferentially retained after gene duplication events, attesting to their importance for signaling [11].

Neuropeptides also appeared early in metazoan evolution [12••,13,14•]. There is considerable conservation of receptor/ligand pairs, indicating a co-evolution of neuromodulatory signaling components [8,12••,13,14•]. A recent phylogenetic analysis of GPCR sequences in the rhodopsin and secretin families showed that invertebrate and vertebrate receptors that were originally thought to have arisen independently are derived from receptors that were present in a common bilaterian ancestor [12••]. Additionally, the core sequences of the corresponding peptide ligands are similar in many instances, suggesting that the basic receptor/peptide relationship has been highly conserved.

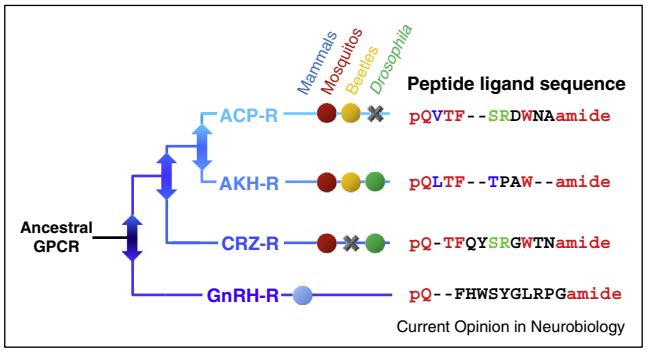
Gene duplications and neofunctionalization has led to diversification of GPCRs and their corresponding peptide

agonists [15••]. Subsequent losses of receptors led to differences in the presence of GPCRs and their corresponding peptide ligands in some lineages [15••]. For example, there are species-differences in the presence of mammalian gonadotropin-releasing hormone (GnRH) receptor homologs and their peptide ligands in insects [16]. It was inferred from the nucleotide sequences that at least three duplications of an ancestral gene led to three different GPCRs in insects (Figure 1). The peptide ligands for these receptors have diverged from each other to the point that they do not activate the other receptors. Thus, these neuropeptides co-evolved with their diverging receptors. Finally, there has been differential loss of the receptors and their corresponding peptides in various insects so that some species, such as mosquitos, have all three receptors, whereas beetles and *Drosophila* have just two [16] (Figure 1).

Monoamine receptors are more promiscuous than neuropeptide receptors; pharmacologically defined receptors are not phylogenetically close to each other [17,18]; serotonin (5-HT), dopamine, and adrenaline (epinephrine) receptors do not segregate on a phylogenetic tree (Figure 2). Thus, the dopamine D1 receptor class is phylogenetically closer to β-adrenergic and 5-HT4 receptors than to D2 receptors [19].

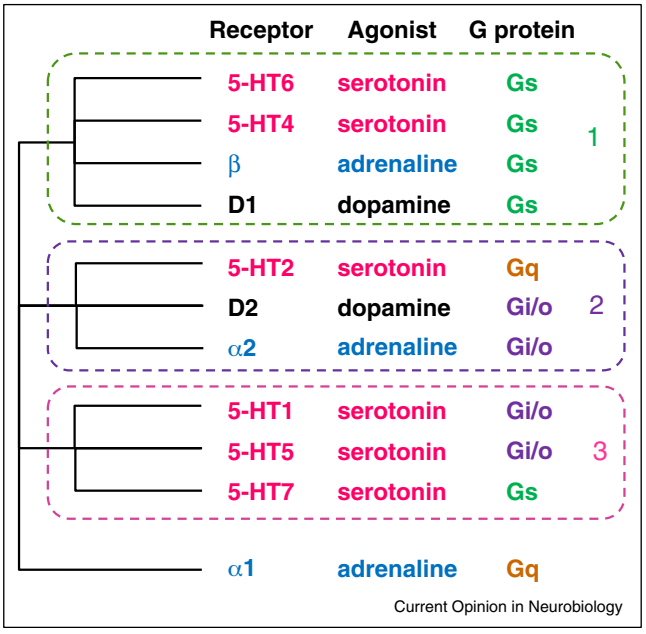
As with neuropeptide receptors, there were several duplication events that led to phylogenetic differences in homologous monoamine receptors. For example, in chordates, D1A receptors are highly conserved both structurally and in localization. However, the D1 class genes have undergone two to four rounds of duplication resulting in the jawed ancestors of vertebrates possibly having four different D1 class receptors. Mammals subsequently lost two of those subclasses, leaving just D1A and D1B receptors, whereas teleost fish underwent a whole genome duplication and now have as many as seven subclasses of D1 receptors [19•].

Figure 1



Evolution of GnRH-related peptides and receptors in insects. Insects have three GPCRs that are related to mammalian gonadotropin-releasing hormone (GnRH) receptors. Peptides and receptors co-evolved through a series of gene duplications (indicated by double arrows), followed by neofunctionalization where the daughter receptors are activated by different peptides. Secondarily, some receptor/peptide pairs have been lost. The circles represent the receptor/peptide pairs that are present in each species. Mosquitos have all three receptors, which are activated by the peptides: corazonin (CRZ), adipokinetic hormone (AKH), and AKH/corazonin-related peptide (ACP). Beetles lost CRZ-R and *Drosophila* lost ACP-R. The three peptides have limited sequence similarity to each other; amino acid residues identical between at least three peptides are highlighted in red, those identical in two peptides are shown as green, and those that are conserved but not identical are indicated in blue. Adapted from [16].

Figure 2



Evolution of monoamine receptors. There are three phylogenetically related groups of monoamine receptors, but they do not cluster by their corresponding ligands. Dopamine receptors are found in both Clade 1 and Clade 2 along with serotonin and adrenaline receptors. The Clades also do not correspond to G protein activation; although Clade 1 receptors all activate Gs, Gs is also activated by the 5-HT7 receptor in Clade 3. Modified from [19].

Conservation versus divergence of functions

The functions of some neuropeptides have been surprisingly conserved. For example, oxytocin and vasopressin play roles in social behaviors in mammals (see Stoop, this issue). The fish ortholog, arginine vasotocin, plays a role in mating behavior [20–22]. Vasotocin levels in birds are associated with gregariousness [23,24]. However, the details of how these peptide/receptor signaling mechanisms act and the specifics of their roles in behavior vary in important ways [25••]. This has led to the notion of a conserved social decision-making circuit in vertebrates [26••], which is a more meaningful way to discuss conserved function because it associates specific networks, rather than ligand/receptor pairs, with behavior. Nonetheless, it is intriguing that vasotocin homologs in invertebrates also