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Short communication

Metabotropic histamine receptors—nothing for invertebrates?

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Abstract

Histamine, a major neurotransmitter both in vertebrates and invertebrates, transmits its actions through a set of well-known receptors. In vertebrates, these receptors belong to the family of G-protein-coupled receptors. In invertebrates, the few well-characterized actions of histamine are transmitted through ionotropic histamine receptors. To evaluate if metabotropic histamine receptors are part of the invertebrate histaminergic signaling cascade, I identified the complete set of metabotropic bioamine receptors from two invertebrates, whose entire genome has been sequenced: the fruitfly *Drosophila melanogaster* and the soil nematode *Caenorhabditis elegans*. A comparison with representatives of all groups of metabotropic bioamine receptors from vertebrates and invertebrates showed that none of these receptors clusters together with any of the four groups of vertebrate histamine receptors. This implies that no direct homologues to vertebrate metabotropic histamine receptor are present in invertebrates. Therefore, it is reasonable to account that the histaminergic neurotransmission in invertebrates is exclusively transmitted through ionotropic histamine receptors and that metabotropic histamine receptors evolved after the split between vertebrates and invertebrates.

Keywords: *Drosophila*; *Caenorhabditis*; Biogenic amine receptor

1. Introduction

The monoamine histamine was among the first compounds recognized as a transmitter/hormone in vertebrates (Kanof and Greengard, 1978). Mediation of inflammatory processes and stimulation of gastric acid secretion are the hallmarks of a histamine's actions. Well-known functions of histamine in the brain comprise regulation of sleep/wakefulness, hormonal secretion, or cardiovascular control (Brown et al., 2001; Schneider et al., 2002). All known effects of histamine are transmitted by only four different metabotropic receptors (Hough, 2001). These receptors, termed histamine H_1, H_2, H_3, and H_4, all belong to the family of G-protein-coupled receptors. In contrast to this comprehensive knowledge about the effects of histamine in vertebrates, much less is known about its role in invertebrates. Nevertheless, histamine gained substantial interest for invertebrate neurobiology because the most interesting synapse in insects and other arthropods, the photoreceptor synapse, uses histamine as its sole transmitter (Hardie, 1987; Stuart, 1999). In addition, histaminergic neurotransmission appears to be required for mechanoreception (Melzig et al., 1996). Other physiological roles of histamine in arthropods are not well documented. The photoreceptor synapse yielded additional attraction after it became obvious that the corresponding histamine receptors are ionotropic, rather than metabotropic (Hardie, 1989). This type of histamine receptor was not known before, and is still believed to represent a peculiarity of arthropods. Recent cloning of these receptors verified their identity as members of the ligand-gated ion channel superfamily (Witte et al., 2002; Gisselmann et al., 2002). The existence of metabotropic histamine receptors was reported several times from different invertebrate preparations, but evidence was not fully satisfying in any of these cases (Roeder, 1990, 1994). Search for metabotropic histamine receptors in different invertebrates is still going on, but the recent breakthroughs in the genome-cloning efforts of metazoan organisms enabled a different approach to solve this problem (Adams et al., 2000; The *C. Elegans* Sequencing Consortium, 1998). To tackle the question if metabotropic (G-protein-coupled) histamine receptors are present in invertebrates, I analyzed all corresponding open reading frames obtained from the completed genome projects of two invertebrate species (*Drosophila melanogaster* and *Caenorhabditis elegans*).

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2. Materials and methods

Among the approximately 19,000 (*C. elegans*) and 14,000 (*Drosophila*) genes, 17 (*C.e.*) and 21 (*D.m.*) genes, respectively, might code for metabotropic bioamine receptors (Table 1). These genes were identified by Basal Local Alignment Search Tool (BLAST) searches using representatives of all groups of vertebrate and invertebrate bioamine receptors. All candidate genes found in both genomes were analyzed using individual BLAST searches (Altschul et al., 1997) and excluded from further studies if they could be placed into other subgroups of this comprehensive protein family (e.g., neuropeptide receptors, olfactory receptors, or rhodopsins). The deduced amino acid sequences of these candidates were compared with those from representative members of all groups of vertebrate and invertebrate metabotropic bioamine receptors, including 5-hydroxytryptamine (5-HT), dopamine, adrenaline, muscarinic acetylcholine, octopamine, tyramine, and, of course, histamine receptors. All sequences were aligned with clustalX (Thompson et al., 1994) and only the conserved regions (especially the transmembrane regions) were used for further analysis. The human rhodopsin and substance P receptor served as outgroups in two independent sets of analysis. Using the PAUP 4.1β10 (Sinauer Associates, Sunderland, MA, USA) program package, it was possible to root the trees and to evaluate the relative homologies between different members of the family of metabotropic bioamine receptors. Trees obtained with both outgroups are identical in their branching pattern. Almost identical results regarding the clustering close to the histamine receptors were obtained using the PHYLIP program package (version 3.6, Felsenstein, 1989).

Table 1
The complete set of metabotropic bioamine receptors from *Drosophila* and *C. elegans*

Annotation	Trivial name	Assignment
C. elegans receptors		
C15B12.5	gar-1	Muscarinic acetylcholine
F47D12.2	gar-2	Muscarinic acetylcholine
C53A5.12	gar-3	Muscarinic acetylcholine receptor
K02F2.6	?	Octopamine receptor
C02D4.2	CeTyrR	Tyramine receptor
C52B11.3		Octopamine receptor
F01E11.5		OAR-like receptor
F59C12.2		5-HT receptor
F15A8.5		Dopamine receptor
M03F4.3		5-HT_7-like receptor
C09B7.1		5-HT_7-like receptor
F14D12.6		5-HT_1-like receptor
K09G1.4		Dopamine D2-like receptor
T14E8.3		Dopamine D2-like receptor
T19A6.A		Bioamine receptor
C24A8.1		Dopamine D2-like receptor
T02E9.3		Bioamine receptor
Drosophila receptors		
CG4356	mAcR-60C	Muscarinic acetylcholine receptor
CG7918		Muscarinic AcR
CG16720	$5\text{-HT}_{1A}/5\text{-HT}_{2A}$	5-HT receptor
CG15113	$5\text{-HT}_{1B}/5\text{-HT}_{2B}$	5-HT receptor
CG1056	5-HT_2	5-HT receptor
CG12073	5-HT7/5-Htdro-1	5-HT receptor
CG8007		5-HT-like
CG3856	OAMB	Octopamine receptor
CG18208		Bioamine receptor/ α-adrenergic-like
CG16766		Bioamine receptor/ α-adrenergic-like
CG7485	Tyr R	Tyramine receptor
CG9652	DopR/DopR1	Dopamine receptor
CG18741	DopR2	Dopamine receptor
CG17004		Dopamine receptor like
CG7994		5-HT_2-like receptor
CG6989		Bioamine receptor
CG7078		Bioamine receptor
CG7431		Bioamine receptor
CG6919		Bioamine receptor
CG13579		Bioamine receptor
CG12796		Bioamine receptor
CG18314		Bioamine receptor

3. Results

A total of 17 and 22 metabotropic bioamine receptors were identified in the genomes of the fruitfly *D. melanogaster* and the soil nematode *C. elegans*, respectively (Table 1). Blast searches with representative members of all classes of metabotropic bioamine receptors revealed no additional members that could be placed into this family. Therefore, it is reasonable to account these two groups of genes as the complete set of metabotropic bioamine receptor genes in *Drosophila* or *C. elegans*, respectively. Members of the 5-HT, dopamine, muscarinic acetylcholine, octopamine, and tyramine receptors (homologues of vertebrate adrenoreceptors) belong to these classes. For a few members of the bioamine receptor family, a direct assignment to one of the groups mentioned above is almost impossible, but even for them, the affiliation to some of these groups could be excluded. Those candidates that cluster in close proximity to any vertebrate metabotropic histamine receptor (H_1–H_4) were analyzed in greater detail.

Subfamilies already known from vertebrate bioamine receptors became also apparent in this study. Based on the phylogeny data (Fig. 1), a total of 17 subgroups could be identified. One of them contains nonclassifiable *Drosophila* and *C. elegans* receptor genes because their natural ligand remained enigmatic. Most of the other groups contain *C. elegans* as well as *Drosophila* receptors, with only few exceptions. One octopamine receptor group contains three *Drosophila* and no *C. elegans* receptor, and a second

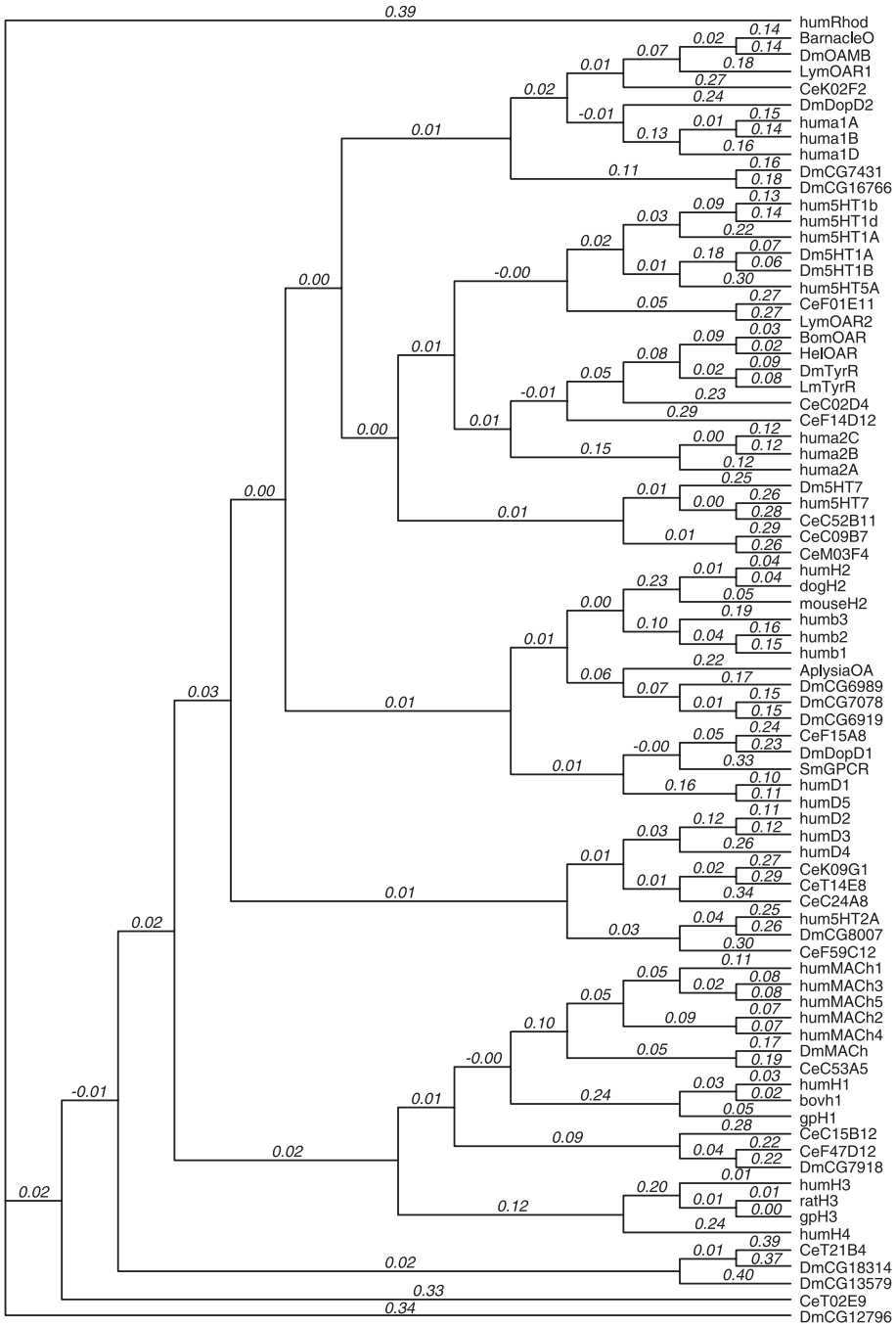

Fig. 1. Phylogenetic tree of all bioamine receptors from *C. elegans* and *Drosophila* and of representative members from all bioamine receptor subgroups from vertebrates and invertebrates. The tree is based on a clustalX aligned matrix and is constructed using the PAUP 4.1β program package. Human rhodopsin and human substance P receptors served as outgroups in independent experiments, yielding almost identical results. The branch length is indicated. Abbreviations: Bom = *Bombyx mori*; bov = bovine; Ce = *Caenorhabditis elegans*; Dm = *Drosophila melanogaster*; gp = guinea pig; H = histamine; Hel = *Heliothis virescens*; hum = human; Lm = *Locusta migratoria*; Lym = *Lymnea stagnalis*; MACh = muscarinic acetylcholine receptor; OAR = octopamine receptor; TyrR = tyramine receptor; 5-HT = 5-hydroxy-tryptamine.

octopamine receptor group contains only one *C. elegans* but no *Drosophila* receptor. Four major groups with invertebrate bioamine receptors could be identified based on the ligand used. These are the dopamine receptor groups (four *C.e.*, two *D.m.*), the 5-HT receptor groups (four *C.e.*, four *D.m.*), the muscarinic acetylcholine receptor groups (three *C.e.*, two *D.m.*), and the octopamine receptor/tyramine receptor/adrenoreceptor group (four *C.e.*, seven *D.m.*).

As already known, 5-HT receptors could be grouped into three subfamilies (5-HT_1, 5-HT_2, and 5-HT_7 families), each harboring both *Drosophila* and *C. elegans* receptors. Among them are the well-characterized *Drosophila* 5-HT receptors

(*Dm*5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_2$, 5-HT$_7$), as well as four yet unidentified receptors from *C. elegans*. The situation for dopamine receptors is comparable, as two large subfamilies, the dopamine D$_{1/5}$ and D$_{2/3/4}$ families, are obviously present. Two *Drosophila* and one *C. elegans* dopamine receptors are already characterized. Receptors from both animals are present in either of the two large dopamine receptor subfamilies, indicating that this divergence is phylogenetically old. The most complex pattern is apparent for adrenoreceptors, establishing groups together with their invertebrate homologues, octopamine receptors and tyramine receptors. The restriction of tyramine receptors and octopamine receptors to invertebrates and of adrenoreceptors to vertebrates obstructs a direct attribution to each other. Nevertheless, octopamine receptor and tyramine receptor subgroups cluster together with adrenoreceptor subfamilies. Conventional octopamine receptors, with the *Drosophila* OAMB (octopamine receptor predominantly expressed in the mushroom bodies) as the archetype, cluster together with other arthropod octopamine receptors, with the snail octopamine receptor 1 (*Lymnea*), the *C. elegans* K02F2.6, and, as the sister group of this assembly, the α_1-adrenoreceptors. Two other *Drosophila* receptors might also belong to this group although their characteristics are yet undetermined. The second, large subgroup is built by the tyramine-type receptors, on one hand, and the α_2-adrenoreceptors, on the other hand. β-Adrenoreceptors show a substantial degree of homology to a group of *Drosophila* receptors that presumably represent octopamine receptor subtypes. A rather strange group made only of two members, an unconventional *Lymnea* octopamine receptor and a yet unidentified *C. elegans* receptor, has no clear-cut vertebrate sister group. The last group of receptors is composed of muscarinic acetylcholine receptors and vertebrate histamine receptors of types 1, 3, and 4. All five different vertebrate muscarinic acetylcholine receptor types (1–5) form a tight subcluster. The sister group of all vertebrate muscarinic acetylcholine receptors is a group composed of one *Drosophila* (*Dm*AChR) and one *C. elegans* (gar-3) receptor. Both receptors are well characterized and known to represent ‘‘classical’’ muscarinic acetylcholine receptors (Hwang et al., 1999). Within this ‘‘muscarinic acetylcholine receptors group,’’ the histamine receptors of classes 1, 3, and 4 are the sister group of the muscarinic acetylcholine receptors mentioned above. In close proximity to this assembly, two receptors from *C. elegans* (gar-1 and gar-2) as well as a *Drosophila* receptor (CG7918) could be identified. Both *C. elegans* receptors were identified as muscarinic acetylcholine receptors following heterologous expression, which is also believed for the *Drosophila* receptor of this group (Lee et al., 1999, 2000). This muscarinic acetylcholine receptors subtree is the group with highest degree of homology to the histamine H$_1$-type receptor group. It contains the vertebrate histamine H$_1$, H$_3$, and H$_4$ receptors. Other invertebrate receptors are not part of this subcluster.

Only very few other invertebrate receptors could not unequivocally be grouped into one of the larger receptor gene families. Among them are some candidates whose bioamine receptor identity is not unequivocal. Nevertheless, there are no indications that these receptors share significant similarities with any of the histamine receptor subgroups, almost excluding their identity as a histamine receptor. Recently, the histamine receptor identity of one putative bioamine receptor from the parasitic flatworm *Schistosoma mansoni* was reported (Ribeiro et al., 2002). Interestingly, this receptor shares no significant homologies with any histamine receptor type of vertebrates.

4. Discussion

An overall comparison of the vertebrate and invertebrate bioamine receptors revealed some interesting insights. The total number of bioamine receptors present in vertebrates (about 30–40) is almost twice as high if compared with the number of receptors found in either the fly (22) or the worm (17). This difference might account for the less complex genome of *Drosophila* and *C. elegans* consisting of about 14,000 and 19,000 genes, respectively, compared with the 30,000–40,000 genes of mice and humans. A greater complexity of the brain and signaling pathways within the brain appears not to be achieved by the greater diversity of bioaminergic signaling. This implies that during evolution of complex brain structures, modular use of already present elements is favored compared with the de novo construction of new elements. On the other hand, small systems such as the nervous systems of worms and flies should share the same basic architecture with the vertebrate brain, making them ideally suited as model organisms for the analysis of basic brain functions.

Besides the different uses of tyramine/octopamine and adrenaline/noradrenaline between invertebrates and vertebrates, the major difference is the obvious lack of metabotropic histamine receptors in invertebrates (at least in worms and flies), which has important implications regarding the nature of histaminergic neurotransmission in arthropods. The histamine-gated chloride channels might be the only receptors transmitting histamine’s actions in invertebrates. Both invertebrates and vertebrates developed these different signaling molecules independently. With respect to the photoreceptor synapse, some important conclusions are apparent. Autoreceptors are required for feedback regulation of transmitter release. They are always G-protein-coupled and located presynaptically. The apparent lack of metabotropic histamine receptors in insects means that this type of feedback regulation could be excluded for neurotransmission at the photoreceptor synapse. It might be useful for this synapse to avoid loss of information through feedback regulation. The sensory information in the visual system covers several orders of magnitude, an issue that has to be optimally represented in the brain, presumably without self-regulatory circuits at the first synapse in this sensory system.

Although studies, especially performed with snails, report the presence of histamine receptor (Steel et al., 1997), these receptors were never characterized on the molecular level. A recent publication reports the identification of a G-protein-coupled receptor from the parasitic flatworm *S. mansoni*, which is sensitive towards histamine application. Unfortunately, pharmacological studies using agonists and antagonists are completely lacking. The preliminary nature of this report allows no decision if histamine is the natural ligand for this receptor or not (Ribeiro et al., 2002). A comparison of its primary structure shows the highest degrees of homology with dopamine and α-adrenoreceptors. Nevertheless, it has to be kept in mind that reports arguing for the existence of metabotropic histamine receptors in invertebrates came from studies performed with members of the lophotrochozoan clade, including molluscs (with snails) and plathelminths (the flatworms). On the other hand, the two model invertebrates, the fly *Drosophila* and the round worm *Caenorhabditis*, are members of the clade ecdysozoa. It is believed that these two lines of invertebrates split very early in animal evolution, close to the point where the deuterostomes (including vertebrates) split from the common ancestor. Therefore, it could not be ruled out that the lophotrochozoa (Adoutte et al., 2000), including snails and flatworms, might indeed harbor metabotropic histamine receptors. As I was not able to find candidates that might represent metabotropic histamine receptors in invertebrates, it could not be ruled out that invertebrates have metabotropic histamine receptors, but if this should be the case, they developed independently after the split between vertebrates and invertebrates. The assumption that histaminergic neurotransmission developed independently between deuterostomes (including vertebrates) and protostomes (invertebrates) was supported by the recent analysis of the *Ciona intestinalis* genome. This ascidian, a primitive chordate, and therewith member of a basal deuterostome line, obviously lacks the enzymes required for histamine synthesis. In addition, I was unable to identify predicted gene homologues to those for metabotropic histamine receptors in the *Ciona* genome. It appears that this primitive chordate has no signaling system that is homologous to the vertebrate histaminergic system of neurotransmission (Dehal et al., 2002), further indicating that systems, including receptors, for histaminergic neurotransmission appeared late in evolution.

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