Molecular biology of insect neuronal GABA receptors

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Ionotropic γ-aminobutyric acid (GABA) receptors are distributed throughout the nervous systems of many insect species. As with their vertebrate counterparts, $GABA_A$ receptors and $GABA_C$ receptors, the binding of GABA to ionotropic insect receptors elicits a rapid, transient opening of anion-selective ion channels which is generally inhibitory. Although insect and vertebrate GABA receptors share a number of structural and functional similarities, their pharmacology differs in several aspects. Recent studies of cloned *Drosophila melanogaster* GABA receptors have clarified the contribution of particular subunits to these differences. Insect ionotropic GABA receptors are also the target of numerous insecticides and an insecticide-resistant form of a *Drosophila* GABA-receptor subunit has enhanced our understanding of the structure–function relationship of one aspect of pharmacology common to both insect and vertebrate GABA receptors, namely antagonism by the plant-derived toxin picrotoxinin.

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IONOTROPIC RECEPTORS for the neurotransmitter γ-aminobutyric acid (GABA) are widespread mediators of rapid neurotransmission in the nervous systems of both vertebrates and invertebrates[1,2]. In these receptors the binding of GABA elicits the rapid gating of an integral chloride-selective ion channel. As the equilibrium potential for chloride ions is usually close to neuronal resting membrane potential, GABA receptor activation may elicit small changes in membrane potential accompanied by powerful, transient, shunts. There are, however, a number of differences in the pharmacology of insect and vertebrate GABA receptors and recent studies of the molecular biology of insect GABA receptors, in particular those of *D. melanogaster*, have provided insight into structures underlying common and distinct aspects of insect and vertebrate GABA receptor function.

Two classes of ionotropic GABA receptors have been observed in vertebrates. $GABA_A$ receptors are antagonized by bicuculline and are found throughout the CNS (Ref. 3), whereas bicuculline-insensitive $GABA_C$ receptors have a more limited distribution[4,5]. $GABA_A$ receptors are regulated by numerous allosteric modulators[3] and display lower agonist sensitivity and faster kinetics than $GABA_C$ receptors which are insensitive to the majority of these modulators[5,6]. However, both classes are blocked by the plant toxin picrotoxinin (PTX).

Although ionotropic insect GABA receptors also gate anion-selective channels and are antagonized by PTX, they do not fit readily into either category of vertebrate ionotropic GABA receptors. Unlike $GABA_A$ receptors, the majority of insect GABA receptors are bicuculline-insensitive[1], yet they differ from both $GABA_A$ receptors and $GABA_C$ receptors in their sensitivity to GABA analogues and allosteric modulators[7–11].

Molecular biology of *Drosophila* GABA-receptor subunits

All ionotropic GABA receptors belong to a superfamily of cys-loop neurotransmitter receptors that includes nicotinic acetylcholine receptors (nAChRs), strychnine-sensitive glycine receptors and serotonin type-3 receptors ($5\text{-}HT_3$ receptors) (Ref. 12). Such receptors are formed by the oligomerization of five subunits around a central, transmitter-gated ion channel. Although cys-loop receptors exhibit great diversity in their pharmacology, their subunits have some remarkably conserved structure–function relationships[12–14]. Thus far, five classes of vertebrate ionotropic GABA receptor subunits have been identified (α, β, γ, δ and ρ subunits), as have multiple isoforms of all the subunits except δ (Refs 3,15). Extensive expression and immunoprecipitation studies suggest that $GABA_A$ receptors are hetero-oligomers of α, β and γ or δ subunits whereas ρ subunits contribute to $GABA_C$ receptors (Refs 3,4,16). To date, three cys-loop receptor subunit classes have been cloned in *D. melanogaster,* with highest sequence identity to vertebrate ionotropic GABA receptor subunits. However, the predicted amino acid sequences of these subunits do not fit readily into the vertebrate GABA receptor classifications. The three known classes are encoded by three genes: (1) *Rdl* (*resistance to dieldrin*; Ref. 17); (2) *Grd* (*GABA and glycine-like receptor of* Drosophila; Ref. 18) and (3) *Lcch3* (*ligand-gated chloride channel homologue 3*; Ref. 19), and the subunits named accordingly, RDL, GRD and LCCH3.

As GABA receptors are widely distributed in the insect nervous system, they are effective targets of both naturally occurring (for example, PTX, Ref. 20) and man-made insecticides (for example, dieldrin, Ref. 20). However, resistance to such insecticides is relatively common in insect populations[21], suggesting a fundamental change in the structure of the GABA receptors of resistant insects. Such a resistant mutant was exploited in the cloning of the *D. melanogaster* GABA receptor gene *Rdl,* which was found to underlie dieldrin resistance in field-isolated strains of *D. melanogaster*[22,23]. The *Rdl* locus maps to position 66F of chromosome III, and by alternative splicing of two of its nine exons[24] gives

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rise to four possible gene products, each of which bears features characteristic of ionotropic GABA receptor subunits (Fig. 1, Box 1). The subunits encoded by *Rdl* are relatively large for members of the cys-loop receptor class (606 amino acids) and display between 30% and 38% identity with vertebrate GABA receptor subunits – about the same percentage identity as seen between the different classes of vertebrate subunit (Fig. 2). Indeed, RDL subunits show similar identity with the α subunits of GlyRs. However, the organization of the *Rdl* gene shares features common to both vertebrate GABA receptors and nAChRs (Ref. 27). Dieldrin resistance in *D. melanogaster* is associated with replacement of a single amino acid (alanine 302 to serine) located in M2, the putative channel-lining domain of RDL subunits. M2 is encoded by exon 7 which is not alternatively spliced.

That a mutation in the *Rdl* gene confers marked insecticide resistance to living *Drosophila*, suggests that the *Rdl*-encoded subunits are likely to be present in many native *Drosophila* GABA receptors. Indeed immunocytochemical studies show that the products of the *Rdl* gene are distributed throughout the central nervous system, although not the musculature, of *D. melanogaster* and are concentrated in regions of neuropil as opposed to those of cell bodies[28–30]. Strong immunoreactivity is detected in the optic lobes, ellipsoid body, fan-shaped body, ventrolateral protocerebrum, glomeruli of the antennal lobes, the mushroom bodies and optic system of the brain of adult *Drosophila,* regions dense with synapses[31,32]; and the distribution of RDL antibody staining correlates closely with that of immunoreactivity for GABA, its synthetic enzyme GAD (glutamic acid decarboxylase)[33,34] and the synaptic vesicle protein synaptotagmin[35]. It therefore seems likely that *Rdl*-encoded subunits contribute to synaptic, neuronal GABA receptors.

RDL-like subunits are not unique to *D. melanogaster* and recently partial and full-length cDNAs encoding homologues of the *Drosophila* subunits have been isolated from a variety of species belonging to three orders of insect. These include the yellow fever mosquito *Aedes aegypti*[36], *Drosophila simulans*[23], and the house fly *Musca domestica* (Diptera)[37], the German cockroach *Blattella germanica* (Dictyoptera)[37,38], and the beetles *Tribolium castaneum*[39] and *Hypothenemus hampei* (Coleoptera)[40]. Over their known sequences, these subunits exhibit a very high amino acid sequence identity to the products of the *Drosophila Rdl* gene (85–99%) and show conservation of the alternative splicing of exon 6. Furthermore, replacements of alanine 302 (with either a serine or a glycine) have been found in all cyclodiene resistant strains examined to date[23,36–40].

GRD and LCCH3 are the other *D. melanogaster* GABA receptor subunits. The *Grd* gene maps to position 75A of the left arm of chromosome 3 and encodes a large polypeptide (614 residues) which displays 33–44% identity with vertebrate GABA receptor subunits, but

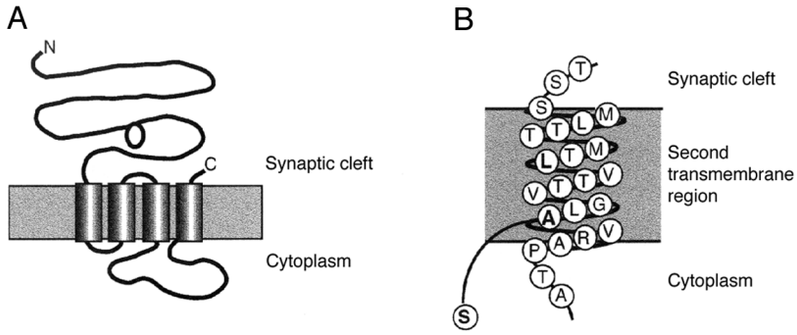

Fig. 1. ***Schematic diagram of an*** **Rdl-encoded Drosophila** ***GABA-receptor subunit.*** **(A)** *The presence of the large extracellularly located N-terminal region, presumed to contain a dicysteine loop, and four transmembrane regions, is characteristic of the cys-loop family of neurotransmitter receptors*[13]. **(B)** *By analogy to vertebrate nAChRs and GABA$_A$ receptors (Refs 12,25), the second transmembrane regions of RDL subunits are presumed to be the principal constituent of the ion-channel lining. The location of the single amino acid substitution (A302S) which underlies cyclodiene resistance is shown in bold, as is the position of the leucine residue found in all GABAR subunits.*

Box 1. Possible roles for the alternative splicing of the *Rdl* gene

Heterologous expression studies have shown that much of the pharmacological and biophysical variation observed in native GABA$_A$ receptors (Ref. a) is attributable to the co-assembly of different subunit isoforms, the majority of which are encoded by separate genes. For example, different α isoforms confer differing GABA and benzodiazepine sensitivity and differing kinetics upon recombinant GABA$_A$ receptors (Refs b,c). The *Drosophila Rdl* gene is unusual in that it is alternatively spliced at two exons, both of which encode regions of the N-terminal domain. As all four possible transcripts of the gene have been observed in *Drosophila* RNA (Ref. d) the question of the functional relevance of this alternative splicing arises. Both the alternatively spliced regions lie close to known determinants of agonist potency in vertebrate GABA receptors, Gly receptors and nACh receptors (Fig. 3) and homo-oligomers composed of the different splice variants do show small differences in their agonist affinity when expressed in *Xenopus* oocytes, illustrating conservation in the structure–function relationships of vertebrate and invertebrate cys-loop receptors. For example, the GABA EC$_{50}$ for RDL$_{ac}$ and RDL$_{bd}$ have been estimated to be between 9–30 μM and 100–150 μM, respectively[e,f]. Although such differences in EC$_{50}$ are relatively small, they are similar to the differences observed with certain isoforms of mammalian GABA$_A$ receptors (Refs g,h,i). Whether such differences in agonist potency are physiologically relevant remains undetermined, and although no difference has been observed in the single channel conductance of RDL$_{ac}$ and RDL$_{bd}$ homo-oligomers[j], the possibility that receptors containing the different *Rdl* splice variants differ in the kinetics of their GABA responses remains to be investigated in detail.

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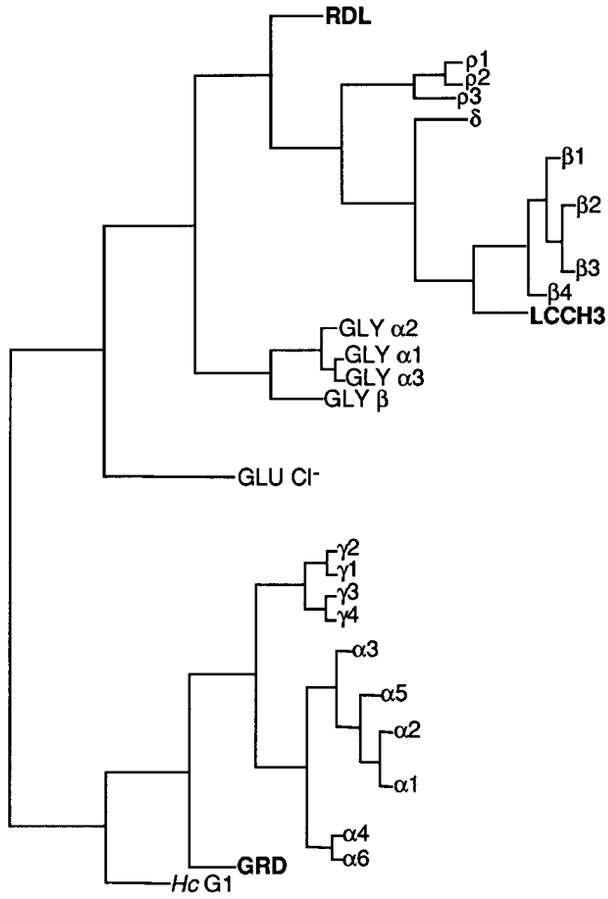

Fig. 2. ***A dendrogram illustrating the relative similarity of the known insect GABA receptor subunits to those of other ligand-gated anion-channels.*** *The PILEUP algorithm (Genetics Computer Group, Madison, WI, USA) was used to group all the known isoforms of these subunits on the basis of similarity in their amino acid sequences. Vertebrate GABA receptor subunits are marked α,β, etc., GLY refers to GlyR subunits while Glu Cl⁻ and* Hc *G1 refer to glutamate-gated chloride-channels and a putative GABAR or GlyR subunit from* Haemonchus contortus[26]. *With the possible exception of* Drosophila *LCCH3, the known insect GABA receptor subunits cannot readily be assigned to any of the vertebrate subunit classes.*

is unique in that it contains a large insertion (75 amino acids) between the conserved dicysteine loop and the first membrane spanning domain[18]. LCCH3, which is encoded by a gene at position 13A on the X chromosome, is smaller than products of *Rdl* and *Grd*, being 476 residues in size, and displays approximately 47% identity with vertebrate $GABA_A$ receptor β subunit isoforms[19]. As such it has been referred to as a *Drosophila* β subunit. LCCH3 also exhibits relatively high sequence identity with a pond snail (*Lymnea stagnalis*) β-like subunit (56% identity)[41]. Homologues of LCCH3 and GRD have yet to be cloned from other insects.

Rdl-encoded subunits confer much of the characteristic pharmacology of insect GABA receptors

D. melanogaster and *A. aegypti Rdl*-encoded subunits readily form functional homo-oligomeric receptors in a variety of expression systems[42–45], the pharmacology of which is unlike that of either class of ionotropic vertebrate GABA receptor, but is similar to that of many GABA receptors found in insect nervous systems. Like the majority of insect GABA receptors, RDL homo-oligomers are unaffected by high concentrations of bicuculline[42,46–48] and are distinguished from both $GABA_A$ receptors and $GABA_C$ receptors by the relative potency and efficacy of GABA analogues[49]. As with native insect receptors, the potency of barbiturate and steroid modulators on RDL (Refs 50,51) is significantly less than that observed on $GABA_A$ receptors.

Like native insect receptors[52,53], the GABA response of RDL homomers[50] is enhanced by the benzodiazepine 4′-chlorodiazepam (Ro5-4864), a non-competitive antagonist of $GABA_A$ receptors (Ref. 54). However the potency of this compound was much reduced on RDL relative to native receptors. Furthermore, flunitrazepam, a benzodiazepine which potentiates many native insect GABA receptors, was without effect on the RDL homomers[47,50]. That the pharmacology of RDL homomers and native insect receptors differ principally in their respective sensitivity to benzodiazepines is striking, as the benzodiazepine sensitivity of recombinant $GABA_A$ receptors is strongly dependent on their subunit composition[3]. Thus, while vertebrate α and β subunit hetero-oligomers form receptors sensitive to GABA, barbiturates and steroids, the co-expression of α, β and γ subunits is a prerequisite for benzodiazepine pharmacology resembling that of $GABA_A$ receptors *in situ*. Indeed determinants of $GABA_A$ receptor benzodiazepine potency have been identified in both α and γ subunits (Fig. 3)[13,55] suggesting that the benzodiazepine-binding site might lie at the interface of these two subunits[14]. This in turn suggests that native bicuculline-insensitive insect GABA receptors may be hetero-oligomers of *Rdl*-encoded subunits and of a second structurally-distinct subunit which has yet to be identified. This is supported by the observation that the single channel properties of heterologously expressed RDL homomers differ from those of GABA receptors on cultured *Drosophila* neurons which are known to express RDL subunits[48,58], although such discrepancies could also reflect differences in the membranes or post-translational modification in homologous or heterologous expression.

GABA receptor diversity in *Drosophila*

As neither LCCH3 nor GRD form functional homo-oligomers in *Xenopus* oocytes[18,48], they probably co-assemble with other subunits to form receptors *in vivo* and are therefore obvious candidates for the suspected missing subunit of RDL-containing receptors. To date, the co-expression of GRD and RDL has not been reported. However, RDL and LCCH3 combine in heterologous systems to form functional receptors with pharmacological and kinetic properties quite distinct from both RDL homo-oligomers[48] and native GABA receptors on cultured *Drosophila* neurones[58], as they are sensitive to bicuculline and insensitive to PTX. RDL and LCCH3 heteromers may be of further use in identifying determinants of bicuculline and PTX action, but these data demonstrate that the missing subunit is not LCCH3. In fact, *Rdl* and *Lcch3*-encoded subunits are unlikely to combine *in vivo*. During embryogenesis, transcription of *Rdl* is observed at stage 13 whereas LCCH3 synthesis is detectable at stage 11[28,29]. Furthermore, the LCCH3 protein is found in the developing neuroblasts of the embryo, and is later confined to the cell body ring of the adult brain[29], whereas RDL is confined to the neuropil and not observed in neuronal cell bodies (Fig. 4)[28,30]. Thus, despite their ability to co-assemble when heterologously

expressed, it seems likely that RDL and LCCH3 subunits contribute to two distinct classes of GABA receptor; it is possible that LCCH3-like subunits might underlie bicuculline-insensitive receptors which have been observed in some insects[59].

Insights into PTX antagonism and insecticide resistance

The replacement of alanine 302 with serine or glycine[27] in all subunits encoded by the *Rdl* gene renders RDL-containing receptors 100-fold less sensitive to PTX than wild-type[42,58]. The A302S substitution affects PTX action in two ways: first it disrupts the antagonist's binding site and second, it affects the mechanism by which PTX stabilizes closed-channel conformations of the receptor[58]. The disruption of the binding site, leading to a reduction in its affinity for PTX, had been inferred from analysis of single-channel studies of wild-type and dieldrin-resistant *Drosophila* GABA receptors[58] and greatly reduces the affinity of a radio-labelled antagonist[60,61]. Compared to GABA receptors on neurones cultured from wild-type (Rdl^{A302}), those of dieldrin-resistant (Rdl^{S302}) strains of *Drosophila* display similar GABA sensitivities, and a small but significant change in channel conductance; however, the A302S substitution stabilizes the channel in an open conformation markedly decreasing the rate of desensitization[58]. That a reduction in the rate of desensitization correlates with a reduction in PTX sensitivity is consistent with the results of several studies of vertebrate and invertebrate GABA receptors. This suggests that PTX acts by allosteric mechanisms, preferentially binding to activated receptors, and stabilizing them in agonist-bound closed conformations[62–65].

RDL residue 302 lies deep in M2, which is considered to be the principal constituent of the ion-channel lining of cys-loop receptors[25]. The amino acid sequences of the M2 regions of GABA receptor and GlyR subunits are highly conserved, allowing the use of a numbering system where RDL residue 302 is assigned position 2′, and the leucine residue found in the M2 of nearly all cys-loop receptors, position 9′ (Ref. 66). As with RDL, the PTX sensitivity of vertebrate GABA receptor and GlyRs is strongly dependent on the amino acid structure of M2. Residues at positions 2′ and 6′ of ρ subunit isoforms alter the PTX sensitivity of $GABA_C$ receptors (Refs 67–69). Similarly, $GABA_A$ receptors are rendered PTX-insensitive by

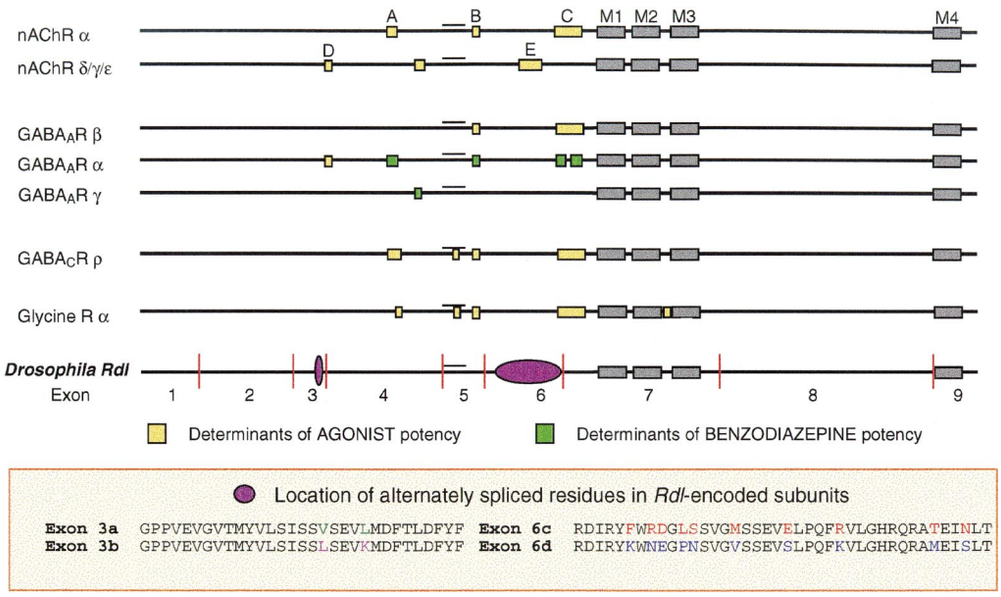

Fig. 3. ***There is a remarkable conservation in the location of the determinants of agonist potency of cys-loop receptors.*** *In this schematic alignment of cys-loop receptor subunits, the location of the cysteine-loop is indicated by the line above the subunit. The location of known determinants of agonist potency in nACh receptors termed loops A–E, are marked yellow, while those of benzodiazepine potency are marked green (see Refs 12–14,55–57). The exon boundaries of* Rdl*-encoded polypeptides are marked by vertical red lines. As a result of the alternative splicing of two exons, the* Drosophila Rdl *gene encodes four polypeptides each of which exhibits characteristic features of GABA receptor subunits. The alternatively spliced exons (3 and 6) encode regions of the extracellular N-terminal domain. There are two variants forms of each exon; those of exon 3 are termed 'a' and 'b' which differ by two residues, while the alternate forms of exon 6, termed 'c' and 'd', differ at ten residues. Thus, depending on the splice variants present in a given polypeptide, the different* Rdl*-encoded subunits may be referred to as* RDL_{ac}, RDL_{bd}, *etc. mRNAs encoding all four splice variants have been identified in embryonic* D. melanogaster[24]. *The positions of these variant residues are marked in purple. The two alternate residues encoded by exon 3 lie close to a known determinant of the agonist potency of* $GABA_A$ *receptors, while the ten variant residues encoded by splice variants of exon 6 span a region which is poorly conserved in vertebrate GABA receptor subunits but which corresponds to determinants of agonist potency in nAChRs.*

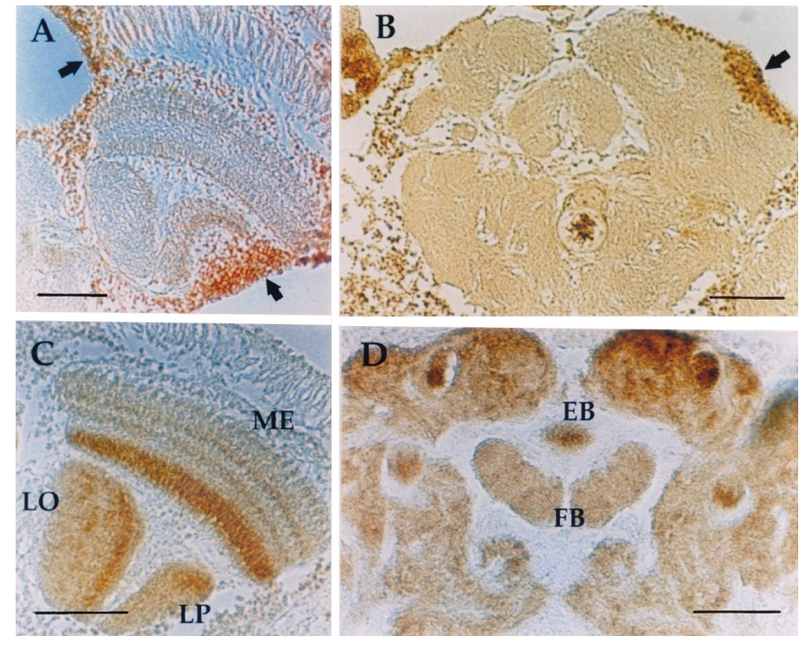

Fig. 4. ***Distribution of RDL and LCCH3 polypeptides in the brain of*** **D. melanogaster.** *Different patterns of immunoreactivity are observed with antibodies raised against RDL and LCCH3 polypeptides. Although the products of both genes are confined to the CNS,* Rdl*-encoded polypeptides are the more widely distributed of the two. Anti-RDL immunoreactivity is confined to regions of neuropil which are dense with synapses, whereas LCCH3 is expressed primarily in the region of neuronal cell bodies.* **(A,B)** *Anti-LCCH3 antibody staining of optic lobe (A) and horizontal section of the central neuropil* (B). *Note the intense staining (arrows) in the cell bodies surrounding the optic neuropil and the supraoesophageal ganglia.* **(C,D)** *Anti-*Rdl *subunit antibody staining in the optic lobe* (C) *and horizontal section of the central neuropil* (D). *Note staining in medulla (ME), lobula (LO) and lobular plates (LP) in* (C) *and ellipsoid body (EB) and fan shaped body (FB) in* (D). From Refs 28 and 29.

replacing the 6′ residue with that found in GlyR β subunits[70]: the unusual M2 region of the GlyR β subunit underlies the PTX insensitivity of native GlyRs (Ref. 71). Using the substituted cysteine accessibility method (SCAM), Akabas and colleagues[25] have suggested that the residues at position 2′ and 6′ of $GABA_A$ receptor α subunits may lie adjacent to each other on the surface of the channel lumen. Furthermore, residue 2′ is less exposed to the lumen in the presence of PTX. The simplest interpretation of the above data is that PTX binds at this part of the channel where it antagonizes GABA-induced currents allosterically. However, the A302S substitution reduces potency in a variety of structurally distinct GABA receptor antagonists[58,61,72–74], some of which interact non-competitively in radioligand binding studies, and may therefore bind to distinct sites on the receptor[75,76]. It is therefore possible that residue 302 contributes directly to a number of overlapping binding sites, or that it influences the structure of these binding sites allosterically. Furthermore, a striking feature of the receptors formed by the co-expression of wild-type RDL and LCCH3 subunits is their insensitivity to PTX (Ref. 48). This result is surprising as both LCCH3 and RDL bear an alanine residue at position 2′, and would therefore be expected to form PTX-sensitive receptors. These data suggest that other regions of the GABA receptor profoundly influence antagonism by PTX and related compounds. In light of this it might be worth noting that recent studies of the mutant GlyR α subunits which underlie hyperekplexia (startle disease) have demonstrated that a single residue at the extracellular end of M2 has a profound effect on both the potency and efficacy of PTX (Ref. 77). It therefore remains to be determined unequivocally where PTX and similar antagonists bind to these receptors.

In conclusion, it is interesting to note that cyclodiene resistance has historically accounted for more than 60% of reported cases of insecticide resistance[21] and is therefore probably one of the most widespread genetic changes selected for by humans. The extreme conservation of this mutation in *Rdl* therefore also raises interesting questions regarding the evolution and spread of insecticide resistance associated mutations. Thus, do resistance associated mutations arise a single time and then spread globally via insect migration, or do different mutational events at the same site occur in different insect populations? Recent studies suggest that the number of independent origins of *Rdl* resistance alleles depends on the life history and migration rate of the insect concerned. For example, the highly mobile fruit fly *Drosophila melanogaster* shows evidence of the global spread of a single mutational event; whereas the less dispersive red flour beetle *Tribolium castaneum* shows clear evidence of multiple origins (D. Andreev, M. Kreitman, R. Beeman, T. Phillips and R. ffrench-Constant, unpublished observations).

Intriguingly, the A302S replacement can persist in insect populations long after insecticide selection has been withdrawn. It may be that plant toxins select for resistance as A302S reduces not only the potency of PTX but also that of picrodendrin plant toxins, a series of PTX-like compounds isolated from the Euphorbiaceae plant, *Picrodendron baccatum*[78]. These plants are known as 'mata bercero' (calf killer) in the Dominican Republic where they have been used to kill bed bugs and lice[79]. Perhaps more interestingly, despite the fact that A302S greatly reduces the rate of GABA receptor desenitization, the fitness of resistant flies does not seem to be decreased. Thus, the only associated behavioural phenotype yet documented for the A302S substitution is temperature-sensitive paralysis[80].

In summary, recent studies indicate that RDL subunits, which have not been identified in vertebrates, are present in many insect species and are likely to be the molecular determinants of much of the distinct pharmacology of bicuculline-insensitive insect GABA receptors. This theory is supported by the widespread anti-RDL immunoreactivity in synaptic regions of *Drosophila* nervous system, and by the fact that the substitution of a single amino acid in *Rdl*-encoded subunits confers resistance to a variety of insecticides. Although, RDL subunits may contribute to the majority of insect GABA receptors, namely those which are insensitive to bicuculline, LCCH3 subunits appear to contribute to a second class of insect GABA receptors which are likely to be antagonized by bicuculline. RDL homo-oligomers, which have already contributed to our understanding of insect GABA receptors as targets for insecticides, offer useful models with which to investigate the structural bases of the distinct pharmacology of bicuculline-insensitive insect GABA receptors. The widespread distribution of *Rdl*-encoded subunits in the *Drosophila* central nervous system may mean that they are also suitable models for other studies, such as those focused on the control of neurotransmitter gene expression and targeting, and it will be of interest to see what effects the mutant forms of RDL subunits have on the behaviour of *Drosophila* beyond the temperature-sensitive paralytic phenotype already documented.

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Principles of acoustic motion detection in animals and man

Hermann Wagner, Dirk Kautz and Iris Poganiatz

Motion provides one of the most important cues for survival, because it helps to break the camouflage of a predator or a prey and because it allows predictions about the future path of an object. Recent data on the processing of acoustic motion have yielded some astonishing findings, suggesting that the psychophysical, neurological and neurophysiological mechanisms underlying the detection and representation of acoustic motion are quite similar to those underlying the detection and representation in other modalities, especially in vision. A further comparison of these similarities and differences with respect to the different environmental constraints posed for the different modalities may help in understanding general problems associated with motion computations.

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SOUNDS ARE ANALYSED in separate frequency channels. The signal in each channel is defined by its frequency, its amplitude and its phase. Thus, dynamic auditory cues can be created by varying any of these parameters alone or varying them in combination. Indeed, sensitivity to frequency modulation has been demonstrated[1–3], as has sensitivity to changes in the most important cues for sound localization, interaural amplitude difference[4–5] and interaural phase difference[6–12]. Despite these data, systematic studies on dynamic auditory cues have so far been rare. The main reason for this could be the absence of convincing psychophysical evidence for neural systems specialized in the detection of acoustic motion. New results[13–15] seem to end a long debate[16] by providing evidence for the existence of specialized acoustic motion-sensitive systems.

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