TIMELINE

100 years of *Drosophila* research and its impact on vertebrate neuroscience: a history lesson for the future

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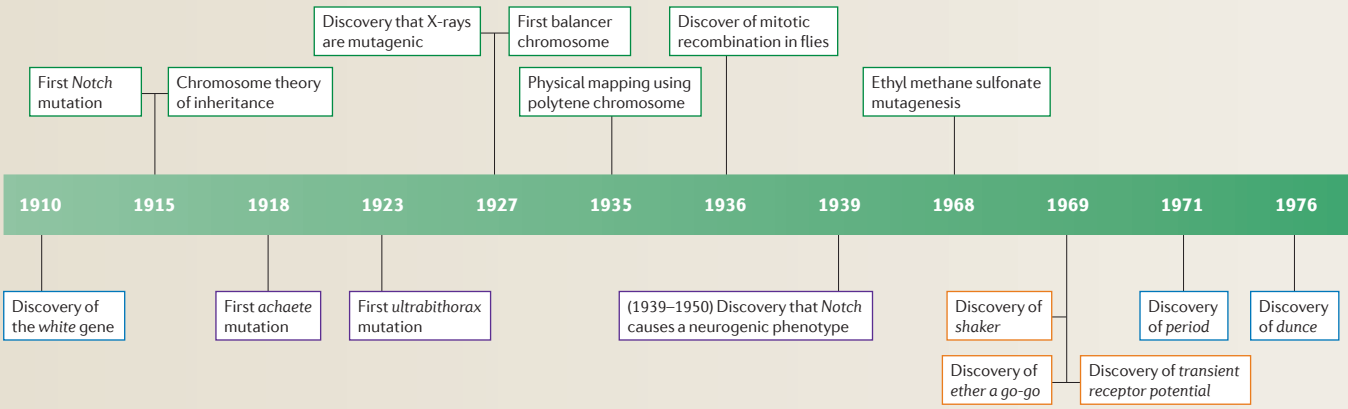
Abstract | Discoveries in fruit flies have greatly contributed to our understanding of neuroscience. The use of an unparalleled wealth of tools, many of which originated between 1910–1960, has enabled milestone discoveries in nervous system development and function. Such findings have triggered and guided many research efforts in vertebrate neuroscience. After 100 years, fruit flies continue to be the choice model system for many neuroscientists. The combinational use of powerful research tools will ensure that this model organism will continue to lead to key discoveries that will impact vertebrate neuroscience.

It was almost 100 years ago that Thomas Hunt Morgan reported the identification of the *white* gene in *Drosophila melanogaster*[1]. Hence, this is an appropriate time to reflect on the past and present contributions of fruit fly research to the field of neuroscience. Genetic approaches dominated the first 50 years of research in *Drosophila* (1910–1960), focusing on dissecting the principles of inheritance[2]. During this time period important concepts and tools were developed that allowed the study of many other biological processes between 1960–2010 (TIMELINE; BOX 1). Indeed, investigators realized in the early fifties that genetic approaches could be used to study problems other than heredity. The continuous development of research tools between 1960–2010 has driven numerous new discoveries in fruit flies. This article highlights the many aspects of nervous system development and function that have been unravelled in fruit flies and how these studies have influenced neuroscience research in vertebrate species.

Development of the nervous system

A pathway to Notch. Mutations in *Notch* were first identified in 1915 and reported in 1916 (REF. 3) as mutations that result in the malformation of wings. It was Poulson who first documented the effects of Notch on embryonic development. Loss of *Notch* causes a so-called 'neurogenic' phenotype, characterized by presumptive hypoderm that differentiates into neuroblasts[4], resulting in an embryo with a hypertrophied CNS at the expense of ventral hypoderm. A systematic search to identify other mutations with similar phenotypes led to the isolation of other key genes that control epidermal versus neuronal fate including *neuralized*, *Delta*, *mastermind*, *big brain* and *Enhancer of split*[5]. The cloning of *Notch*[6] and its ligand *Delta*[7] in the mid-eighties,

Timeline | **Major genes and methodologies discovered in fruit flies**



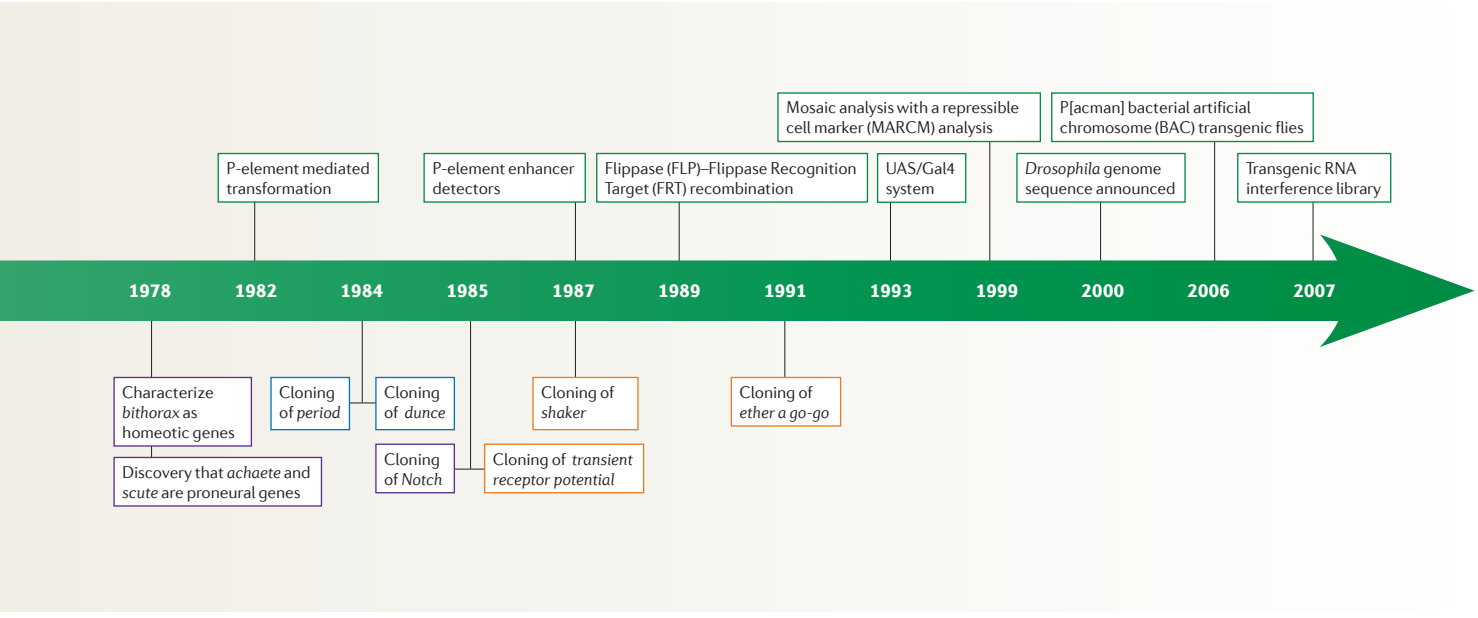
Boxes with green borders indicate the development of important tools and methods; boxes with purple borders indicate the discovey of genes involved in nervous system development; boxes with blue borders indicate events related to genes involved in behaviour; and boxes with orange borders indicate events related to proteins that affect nervous system function. For more details see BOX 1.

as well as the cloning of other key players, helped delineate what is currently known as the Notch signalling pathway[8,9].

Evidence that Notch is conserved in vertebrates resulted from the cloning of the human *NOTCH* gene as the cause of a human leukaemia[10]. In the 1990s it became apparent that the other core components of the Notch pathway that had been identified in *Drosophila* are conserved in vertebrates and that many have similar roles *in vivo*. All the Notch signalling components identified in flies and mammals have been recently compared in detail[11]. The Notch pathway has a seminal role in developmental neurobiology as it affects almost every aspect of neurogenesis and differentiation of neurons in vertebrates, in the developing as well as the adult brain, including neural stem cells[12]. However, the importance of Notch signalling stretches far beyond specifying neuronal versus epidermal cells. Some of its components, including *neuralized*, have now also been shown to have a role in learning and memory formation in adult flies[13]. More importantly, Notch signalling affects neuronal stem-cell specification, blood cell development, heart development, haematopoietic stem cell differentiation, bone and skin development and numerous other tissues. Mutations in the human *NOTCH3* locus (there are four *NOTCH* loci in most vertebrates) cause a devastating neurological disorder named CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy[14]). Finally, aberrant Notch signalling causes several types of cancer[11].

Homeotic genes and vertebrate nervous system segmentation. During the 1950s several scientists realized that existing spontaneous and X-ray induced mutations, such as *achaete*[15] and *Ultrabithorax*[16], which adversely affect the development of an organism can help unravel the principles of development and pattern formation. Lewis focused on the *bithorax* complex of genes and the *polycomb* gene, which are crucial to define the basic segmental identity of the larval and adult thorax and abdomen[17]. Sanchez-Herrero *et al.*[18] showed that the *bithorax* complex contained three genes: *Ultrabithorax*, *Abdominal-A* and *Abdominal-B*. The work on the *bithorax* complex, as well as that on another complex of homeotic genes, the *antennapedia* complex[19,20], led to the discovery that both complexes contain genes encoding evolutionarily conserved homeobox-containing proteins[21] that are involved in DNA-binding and function as transcription factors. Subsequently, the discovery of four large complexes of *homeotic* (*Hox*) genes in vertebrates, with many properties similar to those of *Drosophila Hox* clusters[22], and an important role in patterning the hindbrain[23], had a significant effect on vertebrate neurodevelopmental biology. Furthermore, the *Hox* genes seem to be key for defining the specificity of motor neuron–muscle connectivity[24] and in the genetic programme of neural crest migration[25].

The proneural helix-loop-helix proteins. The *achaete-scute* complex[26] contains a set of four genes (*achaete*, *scute*, *lethal of scute* and *asense)* that had a seminal role in the discovery of the basic-helix-loop-helix (bHLH) transcription factors. These proteins are typically expressed in neuronal precursors of the central and peripheral nervous system (PNS) and are often required to allow ectodermal cells to adopt a neural fate. Mutations in *scute*, which cause a loss of neurons and a loss of bristles or adult sensory structures, were isolated and studied between 1918–1940 (REF. 27). However, in the late seventies, a key set of genetic and developmental observations suggested that *achaete* and *scute* are involved in the initial decision to specify a sensory organ, and not in the differentiation process itself[28,29]. This analysis paved the way for the cloning[30] and identification of proteins encoded by the *achaete-scute* complex. These turned out to correspond to bHLH transcription factors that are expressed in specific domains of ectodermal cells[31] and are required to switch the fate of these cells to neuronal precursors of the PNS — this requirement was also observed for other bHLH proteins such as *Atonal*[32]. The homologues of these genes were then shown to have a key role in vertebrate neurogenesis[33], specification of vertebrate inner ear hair cells[34], touch receptors[35,36] and motorneurons[37]. In summary, the *achaete-scute* complex genes were the founders of an important family of genes required in neural development across phyla[38]. Moreover, apart from the discovery of the bHLH genes, numerous other key genes that affect the development of the external and internal sensory organs in fruit



flies have been identified, including *numb*[39], *cut*[40], *prospero*[41] and *senseless*[42]. Similarly, the vertebrate homologues of these genes (like *Numb* and *Gfi1*) have been shown to affect vertebrate neurogenesis[43–45].

Neurogenesis, neuronal migration and growth cone guidance. In the mid-seventies, the available genetic tools in *Drosophila* (BOX 1) offered an opportunity to address how embryonic pattern formation is controlled and to determine which genes are involved[46]. By carrying out a systematic chemical mutagenesis screen[47] on the different fly chromosomes and analysing the larval cuticular patterns, Nüsslein-Volhard and Wieschaus identified 139 genes that affect the development of fly larvae[48,49]. Although these screens were not designed to identify genes that affect the development or function of the nervous system, they identified many novel players that were later shown to be part of conserved signalling pathways, including genes in the Hedgehog, Wingless, Decapentaplegic or Tumour growth factor-β, and Notch pathways. These pathways are important in vertebrate neurogenesis[50], neuronal migration[51], growth cone guidance[52] and maintenance and differentiation of neural stem cells[53] (TABLE 1). These findings demonstrated the power of forward genetic approaches in solving complex development questions.

Genetic screens in the early nineties also led to the identification of mutations that affect growth cone guidance[54], leading to the discovery of the roundabout or Robo pathway[55]. This pathway controls the crossing of growth cones of pioneering neurons across the midline of the nervous system in flies and mice. Similarly, another set of growth cone guidance proteins that have a repulsive role, the semaphorins, were discovered simultaneously in flies[56] and chick,where the founding member was named collapsin[57]. As is the case for many signalling pathways with pleiotropic roles, these signalling pathways do not only affect growth cone guidance but also other processes such as vascular development and tumour growth in vertebrates[58].

The molecular basis of behaviour

The successful application of genetics to dissect the structure and function of prokaryotic genes in the fifties and sixties prompted Benzer to venture into a new area. He reasoned that as genetics could be used to dissect the principles of inheritance and development, a systematic genetic analysis of fly behaviour should yield genes that control neuronal function. This simple but powerful idea, combined with an efficient protocol for chemical mutagenesis[47], initiated the field of behavioural neurogenetics.

Circadian rhythms. Benzer ventured into this field in 1967 when he described a simple behavioural assay that is still used today: the light countercurrent assay[59], a quantitative method to fractionate populations of flies according to their behavioural responses when exposed to light on repeated trials. He then used ethyl methane sulphonate (EMS) to induce mutations and screened for mutants with defective phototaxis. He isolated several X-chromosome mutations and argued that similar screens and assays could identify mutants that are impaired in gravity, odour or sound perception. This work convinced many of his students and contemporaries that genetics could be used to tackle questions regarding the molecular basis of behaviour that were difficult, if not impossible, to address at the time.

In 1971, Benzer's group published a seminal paper[60] describing a forward genetic screen for defects in the daily rhythm of eclosion and locomotor activity of adult flies. They found three novel mutants affecting a single gene that they named *period* (*per*), which caused faster, slower or complete absence of rhythms (arrhythmic). The identification of the *per* gene took 13 years, largely because the work was published before recombinant DNA technology was a viable research tool[61–64]. Another 13 years passed before human and mouse geneticists identified the corresponding homologues[65]. These studies, together with other forward genetic screens in flies[66] and mice[67,68] led to the isolation of the *timeless* and *clock* genes respectively, laying the groundwork for unraveling the molecular mechanism of the circadian network that is conserved from flies to humans. This work also led to the discovery that mutations in these genes have a role in human disease. Indeed, familial advanced sleep phase syndrome is caused by mutations in the *period homologue 2 (PER2)* and *casein kinase 1 delta (CSNK1D)*, two of the core clock genes in humans[69].

On learning and memory. The development of an olfactory shock-avoidance learning assay in 1974 was another important contribution from the Benzer laboratory[70], resulting in the isolation of the first learning mutant, *dunce* (*dnc*)[71]. Biochemical tests quickly provided compelling evidence that *dnc* mutants were deficient for cAMP phosphodiesterase activity[72,73] and shortly after, *dnc* was shown to encode this enzyme[74]. The role of cAMP in learning and memory was further substantiated with the cloning of the mutant gene of another learning mutant, *rutabaga*, which encodes an adenylate cyclase, an enzyme that produces cAMP[75]. This work laid the foundation for the isolation of many genes that are involved in olfactory learning in *D. melanogaster* and that affect cAMP levels in neurons[76]. A role for cAMP in learning and memory was also documented in *Aplysia californica* in the early eighties[77,78]. This was later confirmed and expanded upon in vertebrates[79]. More recently fly biologists have started to identify changes in calcium dynamics in the olfactory circuitry that correspond well with the behavioural dynamics of olfactory memories[80]. This work is starting to reveal the neuronal mechanisms underlying the storage of memories.

Proteins that affect neuronal function

Tripping on TRP: the transient receptor potential channels. The screens performed by Benzer[59] prompted others to look at EMS-induced mutant flies that had

Box 1 | **Tools and principles developed between 1910–1960**

The most important tools and methods developed in this period include the balancer chromosomes[178,179]. Balancer chromosomes allow investigators to maintain mutations in heterozygous stocks, without having to genotype the animals for further breeding. Hence, mutations in essential genes can easily be studied. *Drosophila* is still the only multicellular organism in which more than 95% of the mutations in essential genes can be maintained easily and effectively.

X-rays were found to be mutagenic and to induce chromosome rearrangements[4] including deletions, duplications, and inversions. The ability to map these rearrangements on salivary gland polytene chromosomes[180] allowed geneticists to physically map genes. Finally, the discovery of mitotic recombination[181] laid the foundation to study the function of essential genes in mosaic animals. Many of the methodologies and reagents created between 1910–1960 have had a major influence on the approaches pursued since the the following decades and have led to the discovery of numerous mutations in loci that are still being studied today.

Table1 | **The roles of Hedgehog, Wingless, Dpp/TFGβ and Notch signalling in the nervous system**

Pathway	Neuronal specification	Neuronal migration	Growth cone guidance	Synapse formation	Neuronal stem cell maintenance
Hedgehog	Mammals[182] and flies[183]	ND	Mammals[182]	Flies[183]	Mammals[182] and flies[184]
Wingless	Mammals[185] and flies[186]	Mammals[185]	Mammals[185]	Mammals[185,187] and flies[188]	Mammals[185]
Dpp/TGFβ	Mammals[189] and flies[190,191]	Mammals[189]	Mammals[189] and flies[192,193]	Mammals[189] and flies[194]	Mammals[195,196] and flies[184]
Notch	Mammals[197] and flies[37,198,199]	Mammals[197]	Flies[200]	Flies[201]	Mammals[184] and flies[184]

Dpp, Decapentaplegic; ND, not determined; TGFβ, Tumour growth factor-β

impaired vision. An electrophysiological assay that had originally been developed in other insects[81] and that records the electrical potentials contributed by many different cell types in the retina upon light stimulation (the electroretinogram (ERG)), allowed the identification of numerous mutants with defects in their light responses[82,83]. One of these mutants caused flies to only exhibit a short transient membrane potential in the ERG upon a flash of light. This mutant later became known as *transient receptor potential* or *trp*[84].

In the early eighties, analysis of genes (and their products) that affect eye signal transduction (rhodopsins, *trp*)[85], pigmentation (*rosy, white*)[86] and development (*sevenless, rough* and many others)[87] were greatly aided by the development of P-element-mediated transformation by Spradling and Rubin[88]. Indeed, Montell *et al.*[89] used this technique to demonstrate that they had cloned the *trp* gene by rescuing the phenotype of mutants *in vivo*. Subsequent sequencing of *trp* revealed that it encoded a light-inducible calcium channel with six transmembrane domains expressed in photoreceptor cells[90]. The Montell laboratory then cloned the first vertebrate TRP channel in 1995 (REF. 91), thereby establishing the presence of a large and interesting family of novel channels in vertebrates[92].

TRP channels are expressed throughout the body and are activated and regulated by multiple stimuli including mechanical stretch, heat, touch and environmental chemicals[93]. TRPs have now been shown to mediate responses to nerve growth factor and pheromones, to affect proprioceptors and touch receptors, to be required for hearing and olfaction in flies, to transduce heat and pain perception, and to affect the transduction of other stimuli, such as osmolarity. Furthermore, mutations in several members of TRP-related channel proteins are responsible for neurodegenerative disorders: mutations in *TRPML1* cause mucolipidosis type IV disease[94], whereas mutations in *TRPV4* cause hereditary motor and sensory neuropathy type IIC[95–97].

Shaking it all: shaker (Sh) and ether-a-go-go (eag). Mutations in *Sh* cause flies to shake their legs when anesthetized with ether[98]. A detailed electrophysiological characterization of these mutants was initiated in the seventies[99,100]. These studies showed that *Sh* mutations cause a prolonged release of neurotransmitters at the larval neuromuscular junction (NMJs) because motor neurons fail to repolarize, suggesting a defect in potassium channels[100–102]. This led to a race to clone and sequence the *Sh* gene[103–106]. The cloning of *Sh* as the first potassium channel allowed its biochemical purification and molecular characterization. Subsequently, a family of at least four *Sh*-related potassium channel genes (*Sh, Shab, Shal* and *Shaw*) was identified in *D. melanogaster* and mammals[107].

Another founding potassium channel member is encoded by the *eag* gene, which was also identified on the basis of its leg-shaking phenotype[98]. In *eag* mutants, neurotransmitter release is enhanced and more prolonged, and in the absence of nerve stimulation, there is a high frequency of spontaneous release[101,108]. *eag* and *Sh* double mutants display a synergistic interaction, suggesting that two different types of potassium channels are involved in the repolarization of the nerve terminal[102]. Cloning and sequencing of *eag*[109] verified this hypothesis, leading to the identification of another family of potassium channels, the so named EAG, ERG (*eag*-related gene) and ELK (*eag*-like potassium) channels[110]. The vertebrate homologue of ERG, HERG, was subsequently linked to a neurological heart disease (LQT syndrome)[111]. Moreover, it was discovered that many commonly used drugs like seldane and vicodin cause cardiac arrythmia by off-target effects on HERG. Obviously, potassium channels have a central role in all neurons[112] and have been implicated in numerous human diseases[113].

Synaptic transmission. The electrophysiological properties of the larval NMJ, a well-established model for studies of synaptic transmission, were first characterized in detail by Jan and Jan. The large size and accessibility of body wall muscles, make them most amenable to electrophysiological[99,114], immunohistochemical[115] and microscopical[116,117 studies]. By being able to manipulate the expression of genes pre- and postsynaptically, these technologies allow the dissection of protein function at an unparalleled level *in vivo*. For example, the study of the role of synaptotagmin at the fly NMJ was the first to provide compelling data *in vivo* that it functions as a calcium sensor for fast synaptic transmission[118]. This was also one of the first examples of using a reverse genetic approach to knockout a gene in *Drosophila*, as no P-element insertion, X-ray or EMS mutants for synaptotagmin were available at the time[119,120]. Similarly, it was first discovered in fruit flies that dynamin, encoded by the fly *shibire* gene[121,122], has a crucial role in endocytosis. Again, the NMJ synapses were seminal in the *in vivo* dissection of the function of dynamin[123,124]. The function of many other proteins required for exo- and endocytosis have been characterized using the fly NMJ, providing important information about the *in vivo* function of many important proteins required for synaptic transmission in vertebrates[125–127]. TABLE 2 details most of the presynaptic proteins that have been studied in fruit flies. Many of these studies were possible because of the coordinated efforts of the Drosophila Gene Disruption Project, which created a large collection of transposable elements that allowed the generation of mutations through imprecise excision, and therefore permitted the detailed functional investigation of many genes[128].

Advantages of studying fruit flies

Drosophila offers many unique advantages that will ensure that it is a premier research organism for many years to come. The

sophisticated manipulations that can be carried out in flies are unsurpassed in any other multicellular model organism[129,130]. These manipulations allow biologists to ask precise questions about behaviour, signalling processes, individual cell behaviours, organ development and adult behaviour. Two experimental key features, namely the successful and efficient removal or addition of single genes or gene products, are important for any model organism to be successfully used in the laboratory. In *Drosophila*, genes can be removed in a random fashion using chemical mutagenesis before screening for specific phenotypes, as already documented[47]. Current tools allow very rapid mapping of chemically-induced mutations that have robust phenotypes, permitting the isolation of null alleles, hypomorphs, hypermorphs, neomorphs and antimorphs as well as conditional alleles, vastly expanding the ability to assess gene function. It is possible to perform a chemical mutagenesis X-chromosome screen and map more than 50 genes in less than a year using duplications and deletions (HJB unpublished data), demonstrating that gene mapping has become almost trivial. Further improvements in speed and accessibility are expected from recent developments related to whole genome sequencing methodologies[131]. These will clearly have a major impact in the mapping of genes that control behaviour. In another approach, one can remove 65% of the fly genes in a targeted fashion using imprecise excisions of transposable elements[128,129]. Alternatively, one can engineer mutations in the locus of interest through selective removal or replacement of sequences, the so-called targeted knockout technology developed originally by Golic and colleagues[132]. Yet another approach is to use RNA interference to reduce the expression of any gene. This methodology works well for some loci and less well for others, but it still offers many possibilities[133,134]. Finally, other methods have been engineered and

Table 2 | **Some of the synaptic vesicle exocytic and endocytic proteins studied in *Drosophila melanogaster***

Protein	Function	Evoked response		Mini EJP amplitude	Ultrastructure		Refs
		1Hz	10Hz		Normal SVs	Large SVs	
Exocytosis							
Cacophony	Presynaptic calcium channel	Low	NA	Normal	?	?	202
Complexin	Clamp/fusion of SV	Low	NA	Normal	Normal	NA	203
CSP	Chaperone for SNAREs	Low	NA	Normal	?	?	204
Hip14	Transport of CSP	Low	NA	Normal	Normal	NA	205
Rop	Docking and fusion of SV	Low	NA	Normal	?	?	206,159
Straightjacket	Targeting of Ca^{2+} channels	Low	NA	Normal	Normal	NA	207
SNAP25	Fusion of SV	Slight reduction	NA	Normal	?	?	208
Synaptobrevin	Fusion of SV	Low	NA	Normal	Normal	NA	150,209
Synaptotagmin	Ca^{2+} sensor	Low	NA	Normal	Normal	NA	119,118
Syntaxin	Fusion of SV	None	NA	None	Normal	NA	210,211,209
Unc-13	Fusion of SV	Low	NA	Reduced	Normal	NA	212
Vha100-1a	Fusion of SV	Very low	NA	Normal/None	Normal	NA	213
Endocytosis							
AP180	Early adaptor	Normal	Low	High	NA	Large	214
Clathrin	SV coat	Normal	Low	Normal	NA	Large	215,216
Dap160	Scaffolding protein	Normal	Low	High	NA	Large	217
Dynamin	Fission of SV	Absent	Absent	Absent	Abnormal	?	218
Endophilin	Recruitment of synaptojanin for uncoating	Normal	Very low	High	Normal	NA	219
Eps15	Scaffolding protein	Normal	Low	Normal	NA	Large	117
Flower	Ca^{2+} channel that couples exocytosis to endocytosis	Normal	Low	High	NA	Large	220
Stoned A or B?	Sorting/recycling	Normal	Low	High	NA	Large	221
Synaptojanin	Clathrin uncoating	Normal	Very low	Not tested	Normal	NA	222
Tweek	PIP_2 delivery	Normal	Low	High	NA	Large	223

CSP, cysteine string protein; EJP, excitatory junction potential; NA, not applicable; PIP_2, phosphatidylinositol biphosphate; SV, synaptic vesicle;?, unknown.

adapted to flies ensuring that *Drosophila* has the most complete arsenal of tools to knock out genes[129].

Adding single genes or gene constructs in flies through P-element-mediated transformation has been available since 1982 (REF. 88). This methodology has been extremely important as it allows the efficient transformation of flies with only a single copy of the DNA of interest — unlike in many other model species — and has permitted some of the most sophisticated manipulations in the animal world[130]. This transformation protocol has recently been improved significantly using P[acman] technology, allowing small to very large pieces of DNA to be inserted in specific docking sites spread throughout the genome[135,136]. Efficient transformation has allowed the development of the flippase (FLIP)–flippase recognition target (FRT) recombination system[137,138], which enables the creation of mutant patches of tissues or cells in an otherwise heterozygous background. It also allowed the development of the UAS/Gal4 system, by which any gene can be expressed ectopically in almost any tissue or cell[139]. Finally, it also led to the development of a high efficiency mitotic recombination system that allows to knockout a gene in specific tissues, organs, cells or neurons and mark the mutant cells[140]. Finally, P[acman] technology allows the tagging of most genes *in vivo*, permitting sophisticated manipulations in a genomic context[141].

In summary, these tools allow the dissection of the function of specific neurons at an unparalleled level of resolution. In addition, current electrophysiological methods allow the functional assessment of numerous different types of synapses including those at the NMJs of fly embryos[142], larvae and adults[99,143], as well as synapses of photoreceptors[81] and the giant fibre system[144]. In addition, several preparations have been developed to record specifically from central neurons[145–148]. Moreover, thousands of UAS/Gal4 lines are now available[149], which allow the modification of gene expression[139], or to functionally[150–153] or physically ablate most neuronal populations in the brain. Finally, the availability of optogenetic tools[154] allows to elicit innate behaviours under the control of a light source. These and many other methods that are currently being developed will ensure that the fruit fly stays at the forefront of neuroscience research for many years to come.

The future of research in the fruit fly

As outlined above, *Drosophila* has and will continue to contribute to many aspects of neuroscience. Current and future research in many areas of fly neurobiology will pave the way to new genes, new pathways and new approaches that will pioneer numerous fields of neurobiology, including vertebrate neurobiology. Obviously, the fruit fly is not suited to study vertebrate-specific issues, such as the development of specific brain structures, regulation of neural crest migration, the function and properties of hippocampal neurons, or to assess how the cerebellum controls motor outputs. However, the fly has the proven potential to provide information about the fundamental features of nervous system organization and function, how information is integrated and processed, how specific genes can cause neurodegeneration, how different brain areas are wired together, and what gene products and genetic cascades control behaviour. Below we list a small sample of recent exciting discoveries to illustrate that research in flies is continuing to be highly influential in neuroscience.

Flies, just like vertebrates, require sleep. Numerous aspects of the physiological properties of sleep are shared between *Drosophila spp*. and humans[155,156], and studies on sleep in flies are paving the way for a better understanding of sleep in vertebrates[157]. Recent genetic screens identified genes that affect the sleep cycle of flies, including mutations in *sleepless*[158]. Sleepless binds to Shaker, suggesting that it modulates Shaker activity by a direct interaction. It seems conceivable that proteins similar to Sleepless, that contain a Ly-6 domain and a glycosylphosphatidylinositol anchor will control sleep in vertebrates[159]. The sleep field is a nice example of how the mammalian community not only 'accepts' discoveries in *D. melanogaster*, but also of how investigators of mammalian systems have turned to flies to advance their research. Indeed, the first genetic screen for sleep genes was actually performed by a mammalian sleep laboratory in collaboration with the Ganetzky laboratory[160]. Similarly, some well-established vertebrate neuroscience laboratories have recently shifted their interest to solving important neuroscience questions in flies[161, 162].

Another example of a recent contribution of research in flies relates to Parkinson's disease , a CNS disease that leads to an impairment of motor skills, speech and other functions. The symptoms result from reduced activity of dopamine-secreting cells of the human substantia nigra[163]. Mutations in a number of genes including α-*synuclein*[164], *parkin*[165] and *PTEN-induced putative kinase 1* (*PINK1*)[166] cause Parkinson's disease, but the mechanisms underlying the disease remain unknown. Studies with mammalian cells have indicated diverse pathogenic mechanisms and disease models, including protein misfolding, abnormal protein accumulation and mitochondrial dysfunction. However, no clear picture has emerged from these studies. The work on *parkin* and *PINK1* mutations in *D. melanogaster*, however, has provided compelling evidence that *PINK1* and *Parkin* are components of a pathway that is involved in regulating mitochondrial remodelling and that mitochondrial dysfunction is a cause of Parkinson's disease[167,168]**.** These, and many other neurodegenerative diseases, including ataxias caused by polyglutamine expansions[169,170], have and will continue to benefit from research in flies[171].

> "Drosophila has and will continue to contribute to many aspects of neuroscience. Current and future research in many areas of fly neurobiology will pave the way to new genes, new pathways and new approaches that will pioneer numerous fields of neurobiology, including vertebrate neurobiology."

Recently, many fly experts have focused their attention on dissecting the molecular and cellular basis of behaviour. These include phototaxis, chemotaxis[172], aggression[173], physical response to mechanical stimuli[174], escape behaviour[175] and sex[176,177]. This focus is illustrated by the concerted efforts of researchers at Janelia Farm, Ashburn, Virginia, USA, who are trying to systematically dissect the origin of every fly neuron, identify different types of adult neurons, the nature of every synapse and the function of different neuronal populations. These studies will undoubtedly advance our understanding of how the nervous system of the fruit fly works and provide us with very valuable paradigms to study mammalian brain function.

As history tends to repeat itself, the main reason for predicting that studies in fruit flies will continue to reveal key aspects of nervous system function is simple: the fly toolbox has an unparalleled sophistication and precision that allows scientists to tackle almost any question in biology and answer it in a timely fashion[129]. Moreover, this toolbox continues to expand quickly[133,135,141,149], ensuring that *D. melanogaster* will remain a model organism of choice for neuroscientists.

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DATABASES

OMIM: http://www.ncbi.nlm.nih.gov/omim
CADASIL | familial advanced sleep phase syndrome | hereditary motor and sensory neuropathy type IIC | LQT syndrome | mucolipidosis type IV disease | Parkinson's disease

FURTHER INFORMATION

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TOC Blurb:

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100 years of Drosophila research and its impact on vertebrate neuroscience: a history lesson for the future

Hugo J. Bellen, Chao Tong and Hiroshi Tsuda

Studies in fruit flies have greatly aided our understanding of the nervous system. Bellen and colleagues take us through the key findings in the last century. They argue that thanks to the unmatched wealth of tools that can be used in *Drosophila melanogaster*, research in flies will continue to contribute to many aspects of vertebrate neuroscience.