Interneurons

Elzbieta Jankowska

In the broadest sense one may consider as interneurons any neurons in pathways between first order sensory neurons and motoneurons. However, usually only neurons with relatively local actions, or relatively short axons, are classified as interneurons. An additional requirement is sometimes that the axons are confined to a given part of the nervous system (a nucleus, one or a couple of segments of the spinal cord, or the gray matter). Which actions are defined as “relatively local,” or axons as “relatively short,” depends on the animal species and the region of the nervous system. For instance, projection neurons of insects have much shorter axons than many neurons considered as typical interneurons of spinal reflex arcs of vertebrates. The latter may project over distances of more than 30 mm and are indistinguishable from other neurons on the mere basis of axonal length or trajectory. In addition, the subdivision of neurons of a given species into “interneurons” and "other types of neurons" is not sharp, because some neurons with long axons, for example, ascending tract neurons, may also act as locally operating interneurons via their initial axon-collaterals.

Like other nerve cells in the central nervous system, interneurons have a wide range of properties and differ morphologically, histochemically, and functionally. Functionally, one may in particular distinguish between excitatory and inhibitory interneurons, between interneurons acting post- or presynaptically and between spiking and nonspiking interneurons. Spiking interneurons operate by generating action potentials (spikes) that are conducted without decrement along the axon and release transmitters from the axon terminals. In contrast, in nonspiking interneurons the transmitter is released as a function of local membrane potential changes that spread electrotonically to the sites of synaptic contacts.

Recent progress in interneuronal studies has been made in three main directions. First, it has become possible to identify interneurons of a number of neuronal networks and to define their characteristic features, including what kind of actions they produce. The most unequivocal way of demonstrating actions of an interneuron is to penetrate it, to stimulate it with intracellular current pulses and to show that it excites or inhibits its target cells ("follower neurons" according to another terminology). An alternative technique ("spike triggered averaging") involves sampling responses of presumed target cells of an interneuron after its extracellularly recorded spikes; the latter may be induced either "spontaneously" or by local application of excitatory amino acids (Jankowska, 1992). Once the characteristic features of interneurons of various networks are established, individual interneurons of these pathways can be recognized, in both vertebrate and invertebrate preparations, and further investigated.

Second, new technical possibilities have opened up in studies of interneuronal properties. For instance, it is now possible to investigate the morphology of selected, functionally identified interneurons after they have been stained with intracellularly applied markers (e.g., Lagerback and Ronnevi, 1982; Lagerback and Kellerth, 1985; Rastad et al., 1990). Immunohistochemical techniques can be used to investigate the type of transmitter synthesized by these neurons or released by fibres that synapse on them (e.g., Maxwell et al., 1997; Geiman et al., 2002) as well as their membrane properties at a molecular level (Carr et al., 1998; Alvarez et al., 1999). Attempts have been made to use some of the approaches that have been fruitful in studies on invertebrates to investigate vertebrate interneuronal systems in vitro. However, these studies have so far been successful in only a small number of preparations of isolated spinal cord of brain slices (see Grillner et al., 1998; Isa et al., 1998; Wenner and O'Donovan, 1999; Roberts, 2000). Attempts have been also made to apply techniques of molecular biology to investigate mechanisms of differentiation of various subpopulations of vertebrate interneurons (e.g., Jessell, 2000; Wenner et al., 2000).

Third, considerable progress has been made in the understanding of the organization of interneuronal systems and their role in various movements. The process has been most spectacular in studies of invertebrates, in particular Aplysia, locust, crab and leech, where neuronal circuits involved in a number of complex reactions (e.g. swimming, jumping, inking or feeding) have been reconstructed and the conditions of their operation, including plastic adjustments, have been defined (Pearson, 1982; Kristan et al., 1988; Burrows, 1992; Selverston et al., 1998; Katz and Harris-Warrick, 1999; Clarac et al., 2000; Jing and Weiss, 2001). Studies in two primitive vertebrate preparations, Xenopus laevis and Lamprey (see Grillner et al., 1998; Roberts, 2000) have been similarly successful. In higher vertebrates, the most advanced have been studies of interneuronal systems subserving movements evoked via the pyramidal tract, spinal reactions including locomotory, scratch, and respiratory movements; the oculomotor systems; and neuronal networks in the cerebellum (e.g. Lundberg, 1979; Shimazu, 1983; Kirkwood et al., 1993; Armstrong et al., 1997; Isa et al., 1998; Barbeau et al., 1999; Burke, 1999). Studies in humans have opened a unique possibility of investigating involvement of spinal interneuronal systems in voluntary movements (e.g., Hultborn et al., 1986; Hultborn et al., 1987; Iles and Pisini, 1992; Pierrot Deseilligny, 1996) and in relating pathologic changes of various interneuronal networks to motor disorders (see Pierrot-Deseilligny et al., 1993; Delwaide and Pennisi, 1994; Jankowska and Hammar, 2002).

In view of the wide range of properties of interneurons in various parts of the nervous system and in various species, it is impossible to generalize conclusions on the mode of operation of interneurons from one population to another. However, the principles of operation of interneuronal systems in various populations, from simple invertebrates to humans, appear to be the same (see Baldissera et al., 1981; Lundberg, 1979; Shimazu, 1983; Barbeau et al., 1999; Burke, 1999; Jankowska and Hammar, 2002).
In all the analysed species, interneurons have been found to play an essential role in integrating information received by the nervous system, and the convergence of primary afferents and fibers of central origin upon interneurons appears to be the rule. Furthermore, the primary afferent input is most often multimodal. Individual interneurons most often have been found to contribute to a number of different reactions (as multifunctional elements of various networks). They therefore may be used to incorporate elements of simple reactions into larger motor complexes, including voluntary movements, to select the most appropriate patterns of motor reactions and to adjust them to the continuously changing environmental conditions.

A change in our views on the role played by interneurons may be illustrated by the interneurons of one of the simplest spinal reflex pathways, the pathway of reciprocal inhibition, in which only one interneuron is interposed between group I muscle spindle afferents and motoneurons. Originally, these interneurons were expected merely to provide a way to change the type of transmitter from excitatory (in synapses made by peripheral afferents) to inhibitory, and to mediate inhibition from one specific group of afferents. It has however been shown that these interneurons function as premotoneuronal integration centers rather than as simple relays (see Baldissera et al., 1981; Jankowska, 1992). They operate as the last link in pathways from a number of various peripheral afferents as well as from supraspinal structures (see Figure 1), the same interneurons mediating inhibition of motoneurons from several sources. Furthermore, the transmission through these interneurons is under both excitatory and inhibitory control, that by Renshaw cells being particularly potent. They can thus be used to adjust the degree of inhibition of various flexors and extensors, so that these muscles can contract either alternately or simultaneously (cocontract).

Systems of control illustrated in Figure 1 operate by excitatory and inhibitory postsynaptic actions. Other control systems involve gating of information reaching interneurons at a presynaptic level and modulation of responses of these interneurons by various modulators. Neuromodulators may change operation of interneuronal networks and their constituent neurons in a very dramatic way. This has been most extensively investigated in invertebrates (e.g., Harris-Warrick et al., 1998; Selverston et al., 1998), but similarly potent effects have been found in vertebrates (see Lundberg, 1982; Jankowska, 2001). Figure 2 illustrates these effects with strong and target-specific effects of norepinephrine on responses evoked in a premotor interneuron in disynaptic pathways from muscle afferents. It shows that locally (ionophoretically) applied norepinephrine prevented the interneuron from responding to nerve impulses from group II (secondary) muscle spindle afferents, although it facilitated its responses from group I afferents. Figure 3 shows that monoamine-releasing neurons may act upon these interneurons along their whole surface, soma and dendrites alike. Effects of norepinephrine and of serotonin on different functional types of neurons and on transmission from different categories of afferents were found to be either similar or opposite (Jankowska et al., 2000) and target specific. Modulators may thus effectively change the way different interneuronal networks operate.

1. See also
   Brain, hierarchical organization [Classic paper]
   Brodmann's areas
   Neuron
   Neocortex, mammalian, ontogenesis
   Cerebral cortex, microchemistry

2. References


**Figure 1.** Simplifying diagram of converging input and target cells of Ia inhibitory interneurons in the cat. *Dark green circle* represents interneurons mediating reciprocal inhibition of flexor motoneurons from extensor muscle spindle primary (group Ia) afferents. *Continuous and dashed lines* indicate monosynaptic and polysynaptic connections from group Ia muscle spindle afferents, low-threshold cutaneous afferents (*cutan.*), high-threshold cutaneous, muscle and joint afferents (*flexor reflex afferents, FRA*) and from rubrospinal, corticospinal, vestibulospinal and propriospinal tract neurons, all excitatory. *i*, ipsilateral; *co*, contralateral. *Blue circles* represent Renshaw cells (*R*) and *light green circle* a population of Ia inhibitory interneurons with opposite actions (in pathways from flexor group Ia afferents to extensor motoneurons), which gate transmission through these interneurons. Neurons mediating presynaptic inhibition of transmission from primary afferents and neurons involved in other modulatory actions (see *Figures 2 and 3*) are not included in this diagram. Modified from Figure 1 in *Lindstrom (1973).*

**Figure 2.** Modulatory effects of norepinephrine (NA) upon intermediate zone midlumbar interneurons in disynaptic pathways from muscle afferents. From top to bottom are examples of responses of an interneuron, afferent volleys and PSTHs of responses evoked before (control), during NA ionophoresis and following a few minutes' recovery. Responses evoked by group I afferents (primary muscle spindle afferents and/or tendon organ afferents) are shown in the *blue frames* while responses evoked from group II afferents (most likely muscle spindle secondaries) are shown in the *green frame*. Modified from Figure 4 in *Jankowska et al., (2000)* with permission from Blackwell Publishing.
Figure 3. Distribution of contacts between Norepinephrine- and serotonin-releasing neurons and an intermediate zone interneuron of the same kind as that illustrated in Figure 2. The interneuron was labelled by intracellularly injected tetramethylrhodamine dextran. The terminals immunoreactive to antibodies against serotonin (5-HT) and dopamine β-hydroxylase (DB-H) were visualised by confocal microscopy, and their distribution at distances 50-800 µm from soma was plotted. Scale 100 µm. Reproduced from Figure 4 in Maxwell et al. (2000) with permission from Blackwell Publishing.