

ON COUPLING AND DECOUPLING OF SPINAL INTERNEURONAL NETWORKS*

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INTRODUCTION

With millions of neurones in the nervous system, and hundreds of synaptic contacts on individual neurones, many steps are needed to investigate their networks. One of the preliminary steps was to define input to and output from a number of neuronal networks, while the content of these networks was considered as a “black box”. This kind of analysis was done for networks sub-serving simple reactions, such as the stretch or withdrawal reflexes, but also for much more complex reactions, such as rhythmic locomotor or scratching movements, or postural adjustments. The next steps involved opening of the black boxes and trying to find out what they contain. This was reasonably easy in the case of networks with only one or two interneurons in series (for references see (28, 47) but much less is known about complex vertebral neuronal networks. The exceptions are networks controlling swimming in one of the most primitive vertebrates, the lamprey (11, 20), or during early stages of the development in the frog (50), although knowledge of such networks in rats (36), zebra fish (38, 49) cats (6, 12, 52) and even humans (48) recently has been greatly advanced.

In the analysis of neuronal networks it is often tempting to follow only one line of connections: from the input to the output of one particular black box. There is however no doubt that individual neurones of one network may be elements of not only one but of several networks, and that a considerable degree of interweaving occurs between the various networks. Currently, we have only a very rudimentary understanding of the conditions under which interneuronal networks operate in conjunction or in isolation and at what level coupling occurs, but several possibilities have been established and will be summarized in the following.

Even in the simplest populations of neurones, those mediating disynaptically and trisynaptically evoked spinal responses (with output neurones A, D and B, C in Figure 1 respectively) a number of coupling sites would be theoretically possible. In the lower part of Figure 1 these facultative coupling sites are indicated by convergence of either direct or indirect input and by collateral actions of the interneurons, which are indicated by the diverging output lines.

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*Review of observations on spinal interneuronal systems most recently investigated in authors' laboratories.

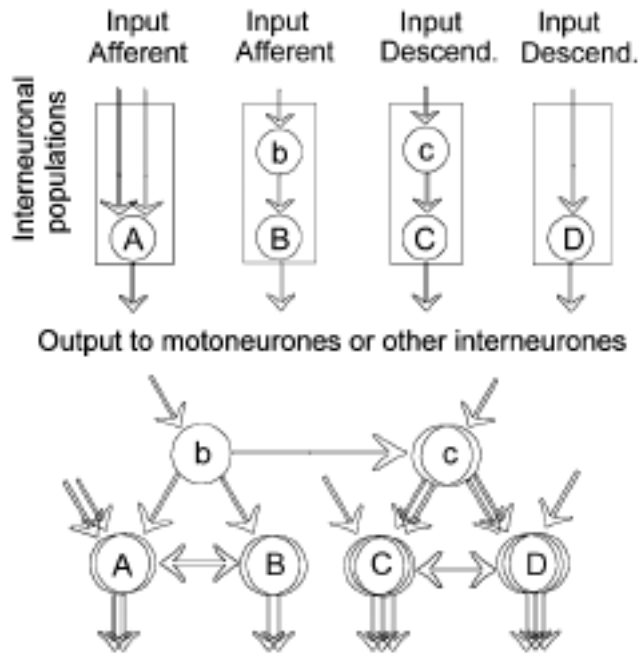


Fig. 1. - Diagrams of 4 simple spinal interneuronal networks including either one (A, D) or two (bB, cC) interneurons in series between afferent fibres or descending tract neurones and motoneurons. Each circle represents a population of interneurons, including both excitatory and inhibitory neurones. Lower panel, interconnections between these networks taking into account collateral projections of their constituent neurones on other interneurons. For the sake of simplicity only some connections are shown.

METHODS

The studies in authors' laboratories were performed in acute experiments on deeply anaesthetised cats and involved the following main approaches: electrophysiological and pharmacological analysis of properties of intracellularly and extracellularly recorded spinal neurones and morphological and immunocytochemical analysis of intracellularly labelled interneurons which had previously been analysed electrophysiologically. Both the preparation and the methods used in these studies are described in the papers cited and in the legends of the figures in which the results are illustrated. All the experimental procedures were approved by Göteborg University Ethics Committee and followed NIH and EU guidelines for animal care.

RESULTS

Coupling via dorsal horn interneurons

One of the networks investigated recently includes premotor intermediate zone interneurons mediating reflex actions of group II muscle afferents on ipsilateral motoneurons. These interneurons are activated both monosynaptically and via dorsal horn interneurons, as indicated in Figure 2A. This arrangement is based on

several kinds of observation. Firstly, on the evidence for existence of 2 populations of interneurons sharing input from group II afferents but differing in a number of ways (9, 16, 30). Secondly, on the demonstration that presynaptic inhibition of transmission to dorsal horn interneurons by GABAergic interneurons (shaded in Figure 2A) is weaker than inhibition of transmission to intermediate zone interneurons (33) and thirdly, that the earlier components of field potentials in the intermediate zone and earliest responses of neurons at this location disappear under influence of presynaptic inhibition, while the later ones are relatively weakly decreased, as illustrated in Figures 2C and G (34). Group II actions evoked at a

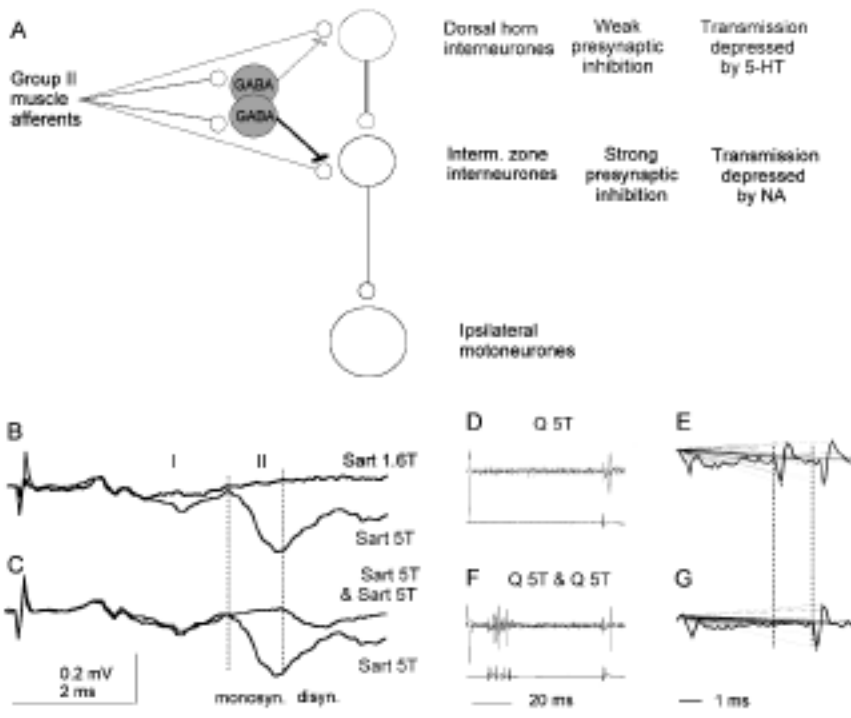


Fig. 2. - Indications of both direct and indirect actions of group II afferents on intermediate zone interneurons, and for mediation of the indirect actions by dorsal horn interneurons.

(A) Diagram of connections between group II afferents and intermediate zone interneurons showing 2 sites at which transmission from these afferents is subject to presynaptic inhibition by GABAergic interneurons (gray) and/or monoamines. (B) examples of field potentials evoked in the intermediate zone by group I (black) and II (orange) afferents. (C) Much weaker depression of the later components of field potentials of group II origin (green) than of the earlier components following conditioning stimulation of group II afferents (D) as a result of differences in presynaptic inhibition at the two sites in A. The two dotted lines indicate onset of monosynaptically and disynaptically evoked potentials. (D-G) Depression of the early but not of the later responses of an intermediate zone interneurone. In (D) and (F) upper traces are averaged extracellular records (n=20) from an interneurone while lower records are from the cord dorsum; the right most parts of these records are expanded in (E) and (G) where the two dotted lines indicate the monosynaptic and disynaptic responses respectively. Modified from Figs. 1, 3 and 6 in (34)

certain delay may thus be attributed to actions mediated by dorsal horn interneurons.

The same arrangement has been found in the network of contralaterally projecting commissural interneurons with group II input (18) indicated in Figure 3A. The records in B and C show EPSPs evoked by group II afferents (orange) in a commissural interneurone projecting to the contralateral GS motor nucleus, the monosynaptic effects eliminated by presynaptic inhibition and only the disynaptic ones remaining after conditioning stimuli were applied (green)., Disynaptic effects on commissural interneurons were attributed to dorsal horn interneurons for the same reasons as those applying to intermediate zone interneurons.

Dorsal horn interneurons may thus be elements of networks formed by both ipsilaterally and contralaterally projecting interneurons with group II input. Dorsal horn interneurons are often co-excited by low and high threshold skin afferents, group III muscle afferents and joint afferents (16) which provide input to a variety of interneurons subserving flexor and extensor reflexes and are collectively termed flexor reflex afferents (FRA, (15). They would thus be elements of the FRA networks as well.

The above conclusions on coupling between various interneuronal populations were supported by analysis of areas of axonal projections of the constituent interneu-

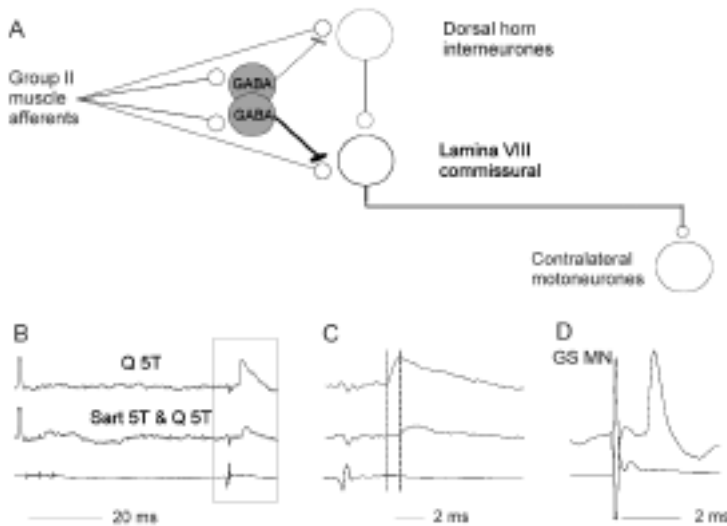


Fig. 3. - Indications for direct and indirect actions of group II afferents on commissural interneurons and for mediation of the indirect actions by dorsal horn interneurons.

(A) Diagram of connections between group II afferents and commissural interneurons showing the two sites at which transmission from these afferents is under presynaptic control as in Figure 2A. (B) and (C) Examples of depression of the early (monosynaptic) but not of the later (disynaptic) components of EPSPs from group II afferents by presynaptic inhibition, with control EPSPs in orange and conditioned EPSPs in green. The right parts of the records in B (in the box) are expanded in C. Averages of intracellular records ($n=20$: top and middle) and of records from the cord dorsum (bottom). Modified from Figs. 1 and 7 in (18, 34).

rones (following intracellular labelling with Neurobiotin). Terminal projection areas of dorsal horn interneurons with group II input were found to overlap with the areas of dendritic branching of ipsilaterally projecting intermediate zone interneurons as well as of contralaterally projecting lamina VIII commissural interneurons (Fig. 4A-D). However, axonal projections of excitatory interneurons were consistently found to extend much less ventrally than of the inhibitory ones. The excitatory interneurons are therefore likely to synapse primarily on dorsally directed dendrites of intermediate zone and lamina VIII interneurons, while actions of inhibitory interneurons might involve both dorsally and ventrally projecting dendrites and cell bodies of these neurons. This would be in contrast to the sites of contacts predicted for reticulospinal tract fibres from their terminal projection areas within the ventral but not dorsal parts of these areas (see (42))

Differential projections of excitatory and inhibitory dorsal horn interneurons were established by comparing axonal arborisations after defining the transmitter content in their terminals using antibodies raised against the vesicular glutamate transporters 1 and 2 (VGLUT1 and 2), glutamic acid decarboxylase (GAD) and either glycine transporter 2 (GlyT2) or gephyrin to identify glutamatergic, GABAergic or glycinergic interneurons respectively as illustrated in Figure 5.

Coupling via premotor interneurons

Coupling between neuronal networks may also occur via premotor interneurons targeting both interneurons and motoneurons. Coupling via premotor interneurons is indicated by double-headed horizontal arrows between cells A and B and cells C and D in Figure 1. Such connections have long been known to exist, e.g. between networks of neurons responsible for recurrent inhibition of motoneurons (Renshaw cells) and interneurons mediating reciprocal inhibition from group Ia afferents (26), or between interneurons mediating reflex actions of group Ib and group II afferents (3, 10, 16, 22). The most recently established coupling of this type is between networks of commissural interneurons with monosynaptic input from reticulospinal neurons (represented by cell D in Figure 1) and networks of interneurons mediating reflex actions of group Ia, Ib and II afferents (13, 32). Such coupling was inferred from occurrence of disynaptic EPSPs or IPSPs evoked in group Ib and II interneurons by stimulation of axons of reticulospinal neurons under conditions when they could only be mediated by commissural interneurons (Fig. 6 C-J). Reticulospinal tract fibres were stimulated within the contralateral medial longitudinal fascicle (MLF) in preparations where only the contralateral spinal half was intact, the ipsilateral spinal half being transected just above the lumbosacral enlargement. In the same preparations disynaptic EPSPs and IPSPs from the contralateral MLF were also evoked in alpha-motoneurons (31), as illustrated in Figure 6A and B. These observations indicate that either individual commissural interneurons or their subpopulations might form synaptic contacts with both motoneurons and other interneurons.

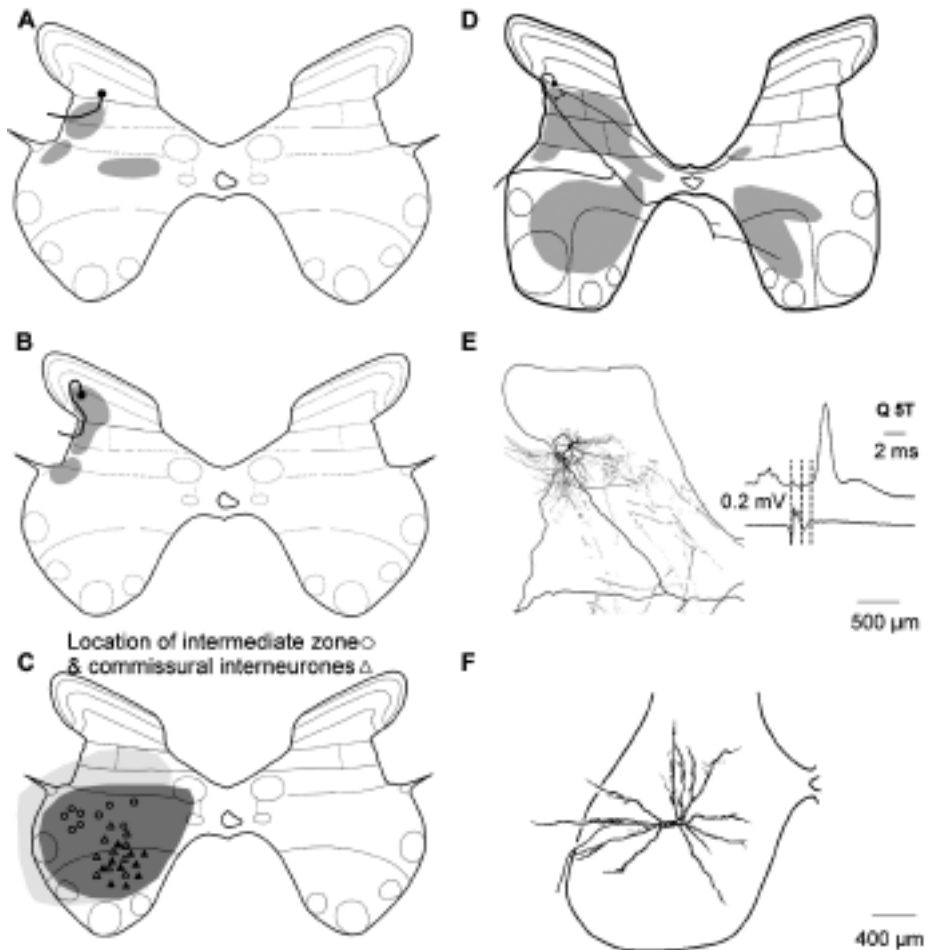


Fig. 4. - *Examples of axonal projection areas of dorsal horn interneurons and of the areas of dendritic extension of intermediate zone interneurons and commissural interneurons.*

Data for interneurons with monosynaptic input from group II muscle afferents which were labelled by Neurobiotin. A, B and D, Locations of somata (filled circles) and projections of dorsal horn interneurons. The shading indicates the areas within which terminals of the excitatory (A, B) and inhibitory (D) interneurons were found. (C) location of somata of intermediate zone interneurons and commissural interneurons (open circles and triangles). The light gray shading approximates to the maximal dendritic spread of intermediate zone interneurons (with an example in F); the dark gray shading approximates to the dendritic spread of lamina VIII commissural cells (modified from (5, 9) and unpublished data). (E), An example of a reconstruction of projection and records from one of the dorsal horn interneurons; modified from (4, 9).

Reconstruction of axonal projections of individual commissural interneurons revealed that their terminal areas were both within and outside contralateral motor nuclei, as illustrated in Figure 7. Projections in Figure 7B and C were as expected to reach Ia interneurons and those in Figure 7 E, F overlapped with the areas of loca-

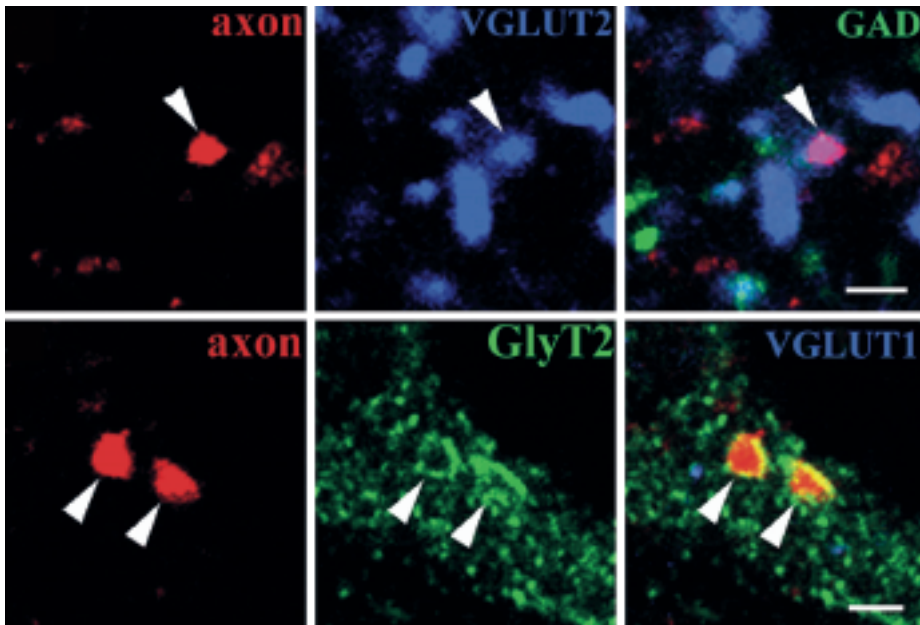


Fig. 5. - *Identification of glutamatergic and glycinergic terminals of dorsal horn interneurons.* Two series of confocal microscope images of terminals from two interneurons. Each image is from a single optical section. Left panels, labelled axon terminals. Middle panels, immunoreactivity for VGLUT2 (blue) and for GlyT2 (green). Right panels, superimposed images showing that the terminals of one of the interneurons were immunoreactive for VGLUT2 (but not for GAD), and of the other for GlyT2 (but not for VGLUT1). Scale bars 2 μ m. Modified from Figs. 2 and 3 in (4).

tion of Ib and group II interneurons. Since all of the labelled commissural interneurons projected to GS motor nuclei in the L7 segment, terminal projection areas within laminae VI and VII in the L4 or L5 segments emphasize this point.

Coupling and decoupling mechanisms

Depending on the strength of input from different sources, only some interneurons of each population may be activated at any given time, allowing certain flexibility in the use of these networks. This flexibility may be further enhanced by selectively strengthening coupling between various network, or by decoupling them. The possibility of independent modulation of transmission via dorsal horn and intermediate zone interneurons (including commissural interneurons (21, 30) in pathways from group II afferents may be of particular importance in this context. Our results indicate that transmission between group II afferents and dorsal horn interneurons is fairly selectively depressed by 5-HT (e.g. at the level of cell b in Figure 1). When this occurs, intermediate zone interneurons (A) become more dependent on their direct group II input, or on input via other intermediate zone interneurons (B) and the coupling between neuronal networks of cells A, B and cells C, D may be tem-

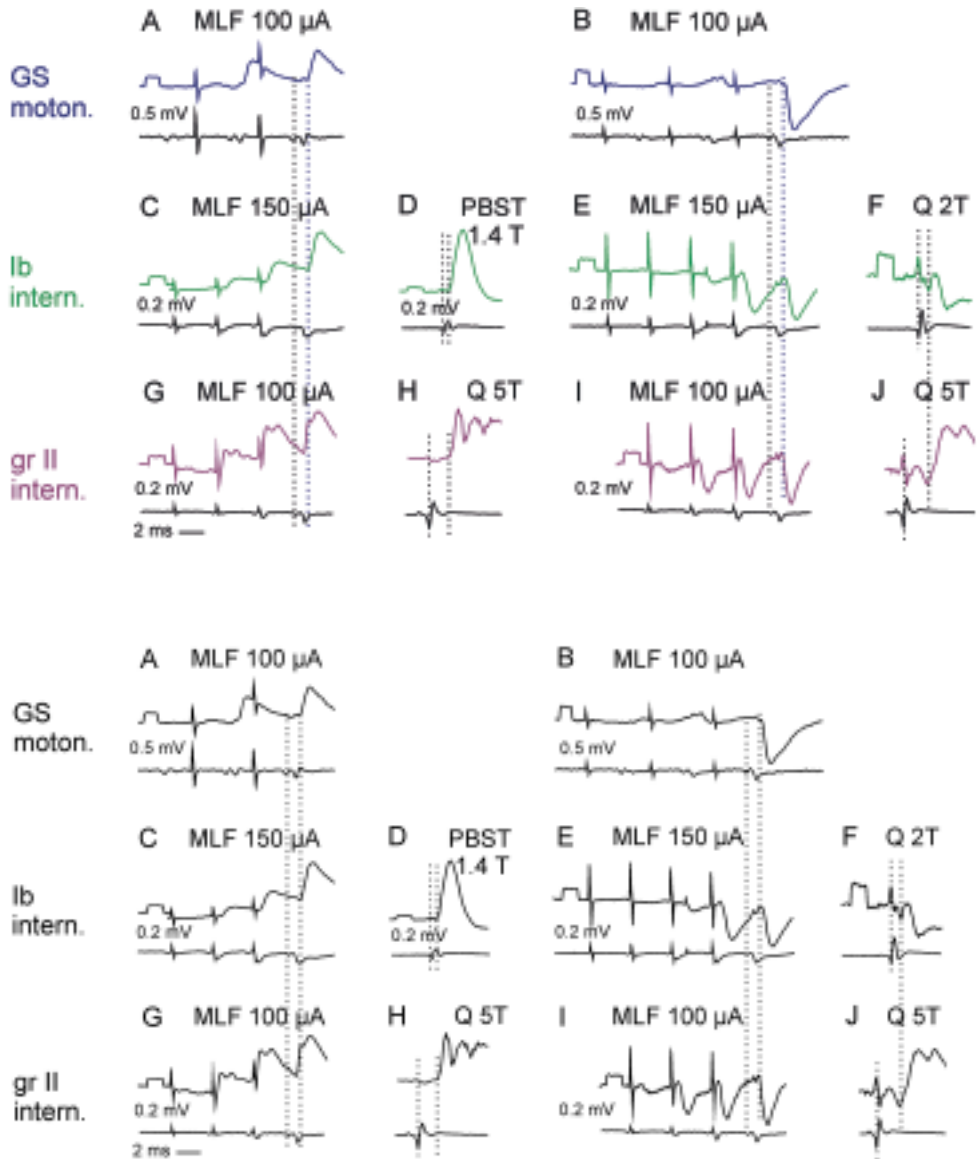


Fig. 6. - Examples of disynaptic PSPs evoked in hindlimb motoneurons and premotor interneurons by stimulation of reticulospinal tract fibres in the MLF via commissural interneurons.

Intracellular records (top traces) from two gastrocnemius-soleus motoneurons (A and B) and four interneurons mediating reflex actions from Ib afferents (C-F) and group II afferents (G-J). Lower traces are from the cord dorsum and show descending and afferent volleys. The records have been aligned with respect to the descending or afferent volleys (indicated by the first dotted lines). The second dotted lines indicate onset of the resulting EPSPs and IPSPs. Note that the latencies of these PSPs with respect to the descending volleys were similar in the motoneurons and the interneurons and that they were compatible with disynaptically evoked actions. Note also that the latencies of EPSPs and IPSPs were similar, indicating direct actions of excitatory and inhibitory commissural interneurons. Modified from Figure 5 in (41) and Figures 3 and 4 in (13).

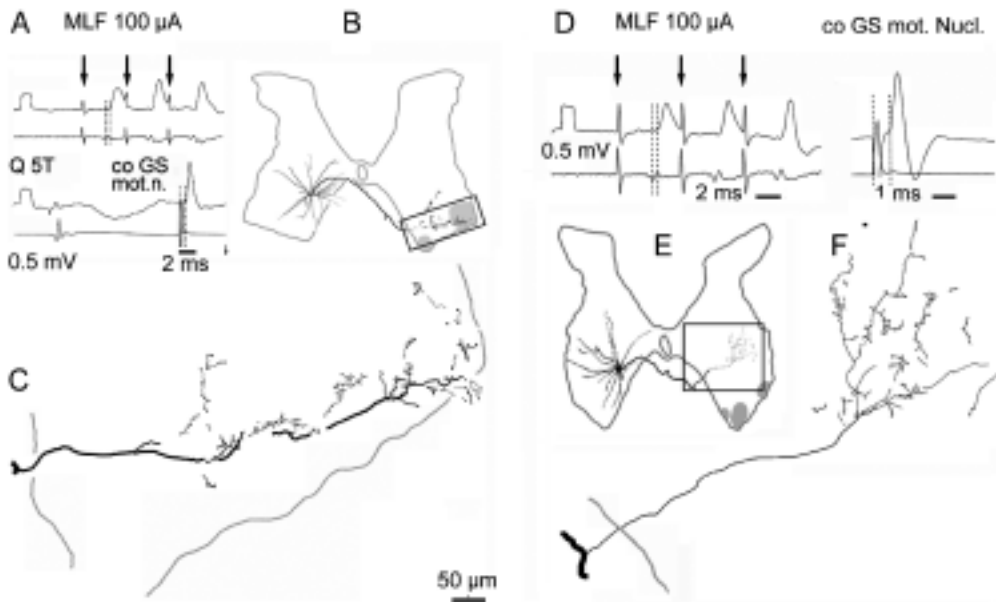


Fig. 7. - Examples of projections of commissural interneurons to the contralateral ventral horn (B, C) and the intermediate zone (E, F).

(A-C) and (D-F) Data for two commissural interneurons with monosynaptic input from the MLF which were antidromically activated from the contralateral gastrocnemius-soleus (GS) motor nuclei (as illustrated in A and D respectively) and intracellularly labelled. (B, C) and (E, F) Reconstructions of dendritic trees and terminal branching areas of these neurons in the L5 and L4 segments respectively. Those in the boxed areas in B and E are shown in more detail in the enlarged reconstructions. Shaded areas indicate motor nuclei. Modified from Figures 7 and 9 in (5).

porarily broken. Consequences of deficits in 5-HT modulatory actions may accordingly be very serious. Some of these have been shown to result in a dramatic change in patterns of coordination of right and left muscle activity, e.g. from inhibition of contralateral motoneurons in preparations with intact supraspinal-spinal connections to excitation of the same motoneurons (and the resulting crossed extension) after spinal injuries that involve axons of descending 5-HT releasing neurones (1).

Conversely, a highly selective depression of transmission between group II afferents and intermediate zone interneurons by NA, combined with strong GABAergic presynaptic inhibition, will make cells represented by cell A in Figure 2 more dependent on disynaptic input via dorsal horn interneurons but will allow joint activation of intermediate zone interneurons A, B, C and D via dorsal horn interneurons b and c. Consequences of deficits in NA modulatory actions may also be very serious because hyperexcitable intermediate zone interneurons with both direct and indirect group II input may provide much stronger than normal input to motoneurons and contribute to exaggerated stretch reflexes. Such deficits may thus be one of the major causes of spasticity (see (48)).

Despite their importance, mechanisms of actions of monoamines on spinal neurones are far from being elucidated. It is in particular not yet known to what extent they are evoked pre- and postsynaptically, both pre- and postsynaptic actions being involved (35, 45, 51). Neither is it known to what extent they are mediated via direct synaptic contacts between NA or 5-HT releasing nerve fibres and postsynaptic cells or presynaptic axon terminals (see (14, 21, 44) or via volume transmission (19). Another question only partly answered is whether their actions are spatially differentiated or involve membrane receptors, or axons terminals in contact with the whole surface of the neurones, or only at particular distances from the cell body.

The latter question was addressed by analysing distribution of appositions of 5-HT and dopamine B-hydroxylase (DBH, to identify noradrenergic terminals) immunoreactive terminals on the surface of dorsal horn, intermediate zone and lamina VIII commissural interneurons (14, 21, 46). The results of these studies revealed generally only minor differences in the coverage of more proximal and distal parts of the dendrites, or of the somata, as illustrated in Figures 8 and 9. However, 5HT₃ receptors on presynaptic terminals appeared to be clustered round some of the somata and were relatively more numerous within the proximal dendritic trees (Fig. 8 A, B). They also revealed generally a low density of contacts of immunoreactive terminals; packing densities of serotonergic (5-HT) immunoreactive terminals were found to be highest on dorsal horn interneurons (Fig. 8F; (16)) that are particularly strongly depressed by serotonin. The density of DBH immunoreactive terminals was only marginally higher on intermediate zone interneurons (46), on which NA has strong depressive actions, when compared with commissural interneurons with input from reticulospinal tract fibres (Fig. 9 F, G; (21)) on which it has facilitatory actions.

The coupling and decoupling between interneuronal networks may also depend on changes in the mode of operation of their constituent neurones. It is still unknown to what extent effects of monoamines on persistent inward sodium or L-type nifedipine sensitive calcium currents found in motoneurons (23, 39) occur in premotor interneurons and, if so, in which types of interneurone. If they do, bistable membrane properties and self-sustained firing (7, 8, 24, 25) associated with the release of monoamines would be expressed in actions of these interneurons on both motoneurons and their target interneurons and would also change the mode of operation of spinal interneuronal networks. It should therefore be of high priority to analyse how monoamines as well as other modulators affect activity of various functional types of interneurons.

Which interneuronal networks are coupled to the network of commissural interneurons.

Reconstructions of axonal projections of commissural interneurons with monosynaptic input from reticulospinal neurones with only exceptional axon collaterals given off before they crossed the midline. However, once they reached the gray matter on the opposite side they branched profusely within as well as outside motor nuclei (5). As illustrated in Figure 7, they branched within areas of location of Ia

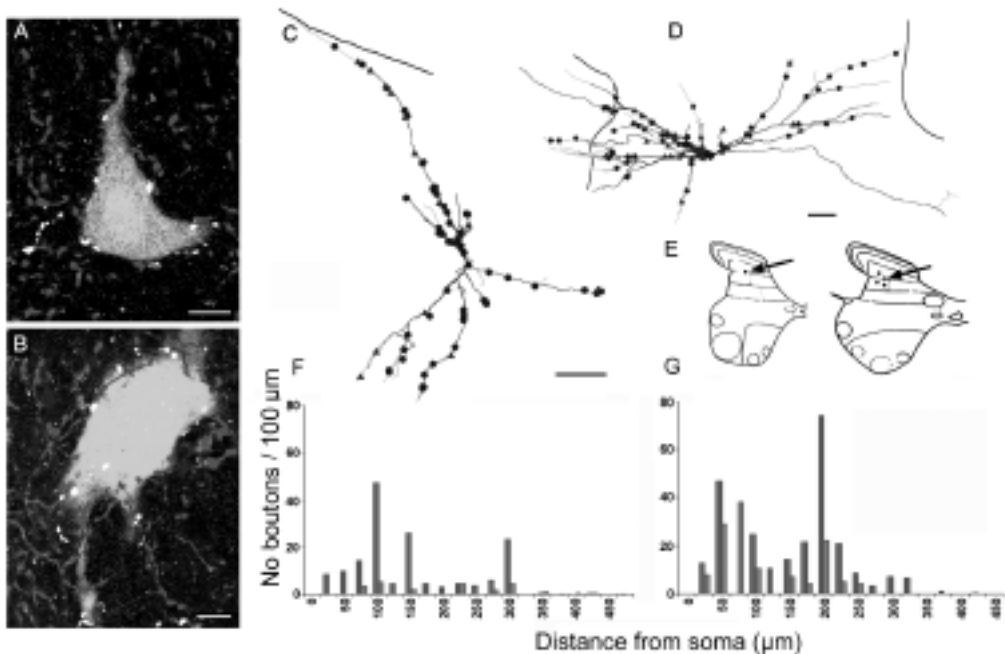


Fig. 8. - Distribution of 5-HT-immunoreactive axons and terminals immunoreactive for 5-HT₃ in apposition to dorsal horn interneurons with input from group II muscle afferents.

(A) and (B) Confocal microscope images of merged single optical sections showing cell bodies of two interneurons (red) with terminals immunoreactive for 5-HT_{3A} receptor subunits (green) and 5-HT (blue). Scale bars 10 μm. (C), (D) and (E), Distribution of contacts formed by 5-HT (red) and 5-HT_{3A} (green) immunoreactive axons along the soma and dendrites of two other interneurons at locations indicated in E. (F) and (G) Scholl plots illustrating distribution of terminal contacts at distances from the soma. Interneuron illustrated in C and F was excitatory. That in D and G was inhibitory. Scale bars 50 μm. Modified from Figs. 6 and 8 in (14).

inhibitory interneurons as well as interneurons mediating reflex actions of group Ib and group II muscle afferents. By recording from these interneurons we have found that commissural interneurons activate contralateral Ia inhibitory interneurons and either excite or inhibit interneurons with monosynaptic input from group Ib and II afferents (13, 32). Disynaptic EPSPs and IPSPs evoked in such interneurons, illustrated in Figure 6C-F and G-J respectively, were evoked by stimulation of reticulospinal tract fibres in the MLF in parallel with disynaptic EPSPs and IPSPs in contralateral motoneurons (Fig. 6A,B). Since they were evoked in preparations in which the spinal cord was hemisected on the side of location of the neurons recorded from, reticulospinal tract neurons could only act via commissural interneurons located on the opposite side. By comparing effects on excitatory and inhibitory actions of group Ib and II afferents on motoneurons it was also demonstrated that excitatory and inhibitory interneurons mediating them are affected in a similar way from the MLF (13). It appeared also that reticulospinal neurons descending on both

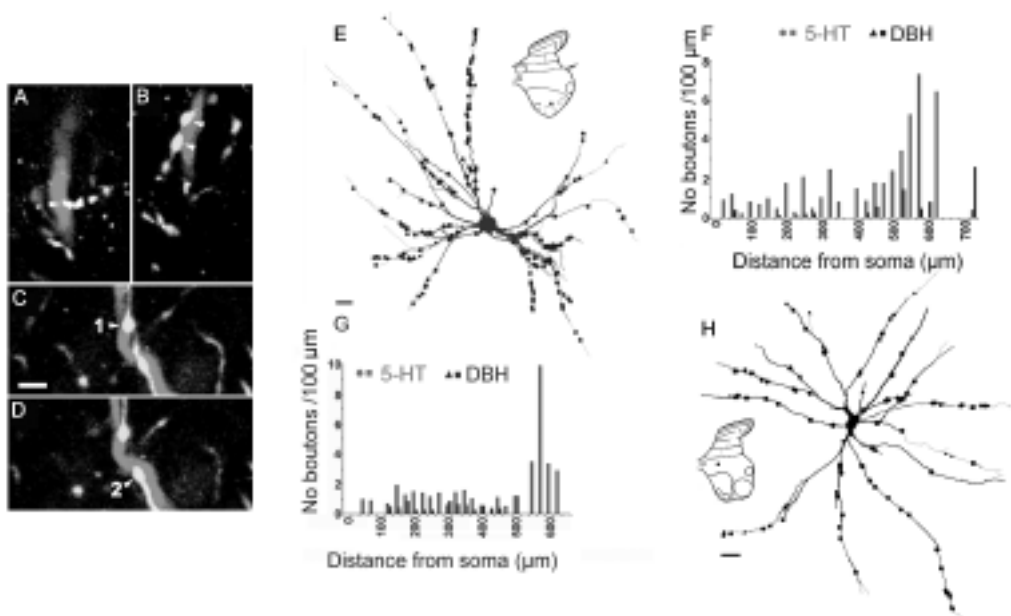


Fig. 9. - Distribution of 5-HT and DBH-immunoreactive axons and terminals in apposition to commissural interneurons with monosynaptic input from reticulospinal tract fibres.

(A-D) Merged confocal microscope images from single optical sections of dendrites of a commissural interneurone (blue), and of terminals immunoreactive for DBH (green) and 5-HT (red). Scale bar 2.5 μm . Modified from Figs. 6 and 8 in (14). (E) and (H), Distribution of contacts formed by the 5-HT and DBH terminals along the soma and dendrites of two interneurons at the indicated locations. (F) and (G), Scholl plots illustrating distribution of these contacts at the indicated distances from the soma. Modified from Figures 7 and 8 in (21).

sides have similar effects (Stecina K. and Jankowska E. unpublished) indicating that networks of Ia inhibitory interneurons and of excitatory and inhibitory group Ib and II interneurons on both sides are coupled via reticulospinal neurones and the commissural interneurons that are activated by them. They are also coupled via pyramidal tract neurones (see (29)) and any other supraspinal neurones that activate reticulospinal neurones and commissural interneurons, e.g. vestibulospinal neurones (37), fastigial neurones (41) and neurones in the mesencephalic locomotor region (43).

GENERAL COMMENTS

It is well established that centrally initiated movements are to a great extent mediated by spinal interneurons and this is true in primates as well as in other vertebrates. Direct actions of supraspinal neurones on motoneurons are of importance, especially for finger precision movements. However, actions on motoneurons alone may not be sufficient for motor reactions to be efficient, and proper motor synergies

may require activation of the whole motor apparatus, including the spinal interneuronal machinery. Quite a lot is known about the contributions of various supraspinal motor systems (e.g. corticospinal, rubrospinal, reticulospinal or vestibulospinal) to movements. However, knowledge of how activation of spinal interneuronal networks targeted by supraspinal neurones is integrated is rather patchy, even for those neurones analysed in most detail. For instance, integration of actions of corticospinal, rubrospinal, tectospinal and reticulospinal neurones at the level of propriospinal neurones in the C3-4 segments and their importance for visually guided reaching movements have been very extensively investigated (for references see (2, 40)). However, little is still known on how activation of these propriospinal neurones is integrated with activation of segmental interneurons that mediate object grasping and retrieval, or of neuronal systems that ensure postural adjustments. Even less is known about the extent to which the C3-4 propriospinal neurones are involved in mediating actions of corticospinal, reticulospinal and other supraspinal neurones on lumbo-sacral motoneurons. Likewise, it has long been established that excitation of one muscle group by corticospinal neurones may be associated with activation of Ia interneurons that lower the probability of activation of their antagonists, and that Ia interneurons may also be excited by other descending tract neurones (for references see (27, 32)). However, coupling between the network of Ia interneurons and of the network of commissural interneurons activated by reticulospinal neurones and corticospinal neurones has been determined only recently (17, 32) and much more remains to be discovered about them. Very little is also known about how the networks and coupling mechanisms discussed here are deployed in various movements and what other neuronal networks might be involved. As usual, finding answers to some questions raises many more questions to be answered.

SUMMARY

This review addresses the question of interrelations between spinal interneuronal networks. On the basis of electrophysiological, pharmacological, morphological and immunohistochemical analysis of interneurons mediating various reflex actions from muscle receptors and of reticulospinal neurones a considerable degree of interweaving between networks of these neurones has been established. The coupling has been found to occur at the level of several sites of these networks but the review focuses on two of these sites. The first is between dorsal horn interneurons with group II input and their target ipsilaterally and contralaterally projecting intermediate zone and commissural interneurons. The second is between commissural interneurons with input from reticulospinal neurones and their target interneurons. Several ways of both strengthening and weakening of coupling between various interneuronal networks are also briefly reviewed.

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