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Spinal reflexes, mechanisms and concepts: From Eccles to Lundberg and beyond

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Abstract

This review focuses on investigations by Sir John Eccles and co-workers in Canberra, AUS in the 1950s, in which they used intracellular recordings to unravel the organization of neuronal networks in the cat spinal cord. Five classical spinal reflexes are emphasized: recurrent inhibition of motoneurons via motor axon collaterals and Renshaw cells, pathways from muscle spindles and Golgi tendon organs, presynaptic inhibition, and the flexor reflex. To set the scene for these major achievements I first provide a brief account of the understanding of the spinal cord in ‘‘reflex’’ and ‘‘voluntary’’ motor activities from the beginning of the 20th century. Next, subsequent work is reviewed on the convergence on spinal interneurons from segmental sensory afferents and descending motor pathways, much of which was performed and inspired by Anders Lundberg's group in Gothenburg, SWE. This work was the keystone for new hypotheses on the role of spinal circuits in normal motor control. Such hypotheses were later tested under more natural conditions; either by recording directly from interneurons in reduced animal preparations or by use of indirect non-invasive techniques in humans performing normal movements. Some of this latter work is also reviewed. These developments would not have been possible without the preceding work on spinal reflexes by Eccles and Lundberg. Finally, there is discussion of how Eccles' work on spinal reflexes remains central (1) as new techniques are introduced on direct recording from interneurons in behaving animals; (2) in experiments on plastic neuronal changes in relation to motor learning and neurorehabilitation; (3) in experiments on transgenic animals uncovering aspects of human pathophysiology; and (4) in evaluating the function of genetically identified classes of neurons in studies on the development of the spinal cord.

Keywords: Intracellular recording; Motor control; Spinal cord; Spinal interneurons; Spinal reflexes; Supraspinal control

Contents

1. Introduction

Three of the chapters in this series of articles describing the lasting importance of the work by Sir John Carew Eccles (1903–1997) are authored by his co-workers from Eccles'

Abbreviations: CNS, central nervous system; EPSP, excitatory postsynaptic potential; FRA, flexor reflex afferents; IPSP, inhibitory postsynaptic potential; MLR, mesencephalic locomotor region

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"golden period" in Canberra, AUS from 1952–1966 (Andersen, 2006; Ito, 2006; Willis, 2006). This is not the case for my chapter, although I am of proud of being a member of Eccles' "scientific lineage". I had the privilege to meet him at several scientific meetings; mainly after his move to Contra, CHE in 1976. In June 1986, Eccles made a short visit to Copenhagen, with his wife Helena, where he gave a lecture to the Medical Faculty, University of Copenhagen under the auspices of the newly formed Danish Society for Neuroscience. We enjoyed having both of them for lunch at the Faculty Club, and at my home for a private dinner that night. Eccles was relaxed, and he enjoyed entertaining the young scientists who were present in my laboratory not long after I had moved to Copenhagen from Anders Lundberg's group in Gothenburg.

Most of the articles from Eccles' time in Canberra are so well-known, and reviewed so many times, that the description of these results here will be kept rather short and concise. Rather, more emphasis is focused here on what Eccles' contributions meant for subsequent steps in the scientific development of the field of "spinal cord and motor control".

In order to give an idea of the background for Eccles' contribution to and impact on the field, I begin by describing the development during the last century of conceptual views on central motor control and relevant methodological advancements. The major part of this review then covers the analysis of five specific spinal neuronal pathways, where Eccles' contributions during his Canberra period have been of particular importance. In Section 4, the development of ideas from the time before Eccles entered the scene will be described, and then followed up to the present. I end with some comments on future potential advancements and possibilities in the field (Section 5).

2. Development of conceptual views during the last century on the role of the spinal cord in "reflex" and "voluntary" motor activities

I wish to begin with a citation from Sir Michael Foster (1836–1907) in his renowned textbook of physiology (Foster, 1879). There he wrote that "... reflex action may be said to be, par excellence, the function of the spinal cord" (quoted on p. 98 in Liddell, 1960), but added that "the cord contains a number of more or less complicated mechanisms capable of producing, as reflex results, coordinated movement altogether similar to those which are called forth by the will. Now it must be an economy to the body, that the will should make use of these mechanisms already present, by acting directly on their centres, rather than it should have recourse to a special apparatus of its own of a similar kind" (p. 101 in Liddell, 1960). Actually this opinion is not too far from the view of Sir Charles Sherrington (1857–1952), that reflexes are "the unit reactions in nervous integration" (Sherrington, 1906). He thought that a simple reflex "... is probably a purely abstract conception, because all parts of the nervous system are connected together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts" (p. 7). He also thought of the simple reflex as "... a convenient, if not a probable, fiction" (p. 7) in the study of the coordination of more complex "compound" and "allied" reflexes, and noted that under normal circumstances (without spinalization or decerebration) "... a reflex detached from the general nervous condition is hardly realizable" (p. 117).

Although the above Sherrington quotes are from his book "The Integrative Action of the Nervous System", which was published in the early 1900s (Sherrington, 1906), I believe that they reflect the conceptual scene at the University of Oxford, GBR when Eccles arrived there in 1925, first entering the Final Honours School, and later joining Sherrington in a series of experiments from 1928 to 1932. During his first years at Oxford, Eccles also worked with Edward Liddell (1895–1981), Derek Denny-Brown (1901–1981), Stephen Creed (1898–1964), and Ragnar Granit (1900–1991). Most of Eccles' work in this period (particularly with Creed, Granit, and Sherrington) dealt with flexor reflexes, the crossed extensor reflex, and their interactions. They examined the time course of the "central excitatory state" (c.e.s) which Sherrington thought reflected the excitation of the motoneurons by afferent volleys (see Brownstone, 2006). Similarly they studied the active "central inhibitory state" (c.i.s) associated with the inhibition of flexor reflexes by volleys in contralateral nerves. It was on the basis of these studies that Eccles became a co-author of the influential monograph "Reflex Activity of the Spinal Cord" (Creed et al., 1932), which summarized the work from the "Sherrington School" over many years. It was in 1932 that Sherrington shared the Nobel Prize with Lord Edgar Adrian (1889–1977) "for their discoveries regarding the functions of neurons". Sherrington's Nobel Lecture was entitled "Inhibition as a coordinative factor". It focused on inhibition as a central and active process, which interacts with excitation.

During Eccles' subsequent period in Sydney, AUS (1937–43) he continued his last work from Oxford on synaptic transmission in sympathetic ganglion and the neuromuscular junction (see Stuart and Pierce, 2006). By the end of this period he had reached the conclusion that synaptic transmission in these two cases (in the peripheral nervous system) was chemical rather than electrical. In Dunedin, NZL (1944–1951) Eccles returned to the spinal cord primarily with the aim of studying the excitatory and inhibitory synaptic transmission in the central nervous system (CNS). He started out by refining his hypothesis of electrical transmission for excitation and inhibition and then putting it to an experimental test. With the introduction of intracellular recording (see Brownstone, 2006) he proved himself to be wrong; his own intracellular recordings from motoneurons left no doubt that transmission was chemical. The work from these periods in Sydney and Dunedin are summarized in Eccles' Waynflete Lectures delivered in Oxford in 1952, and shortly afterwards published in his book "The Neurophysiological Basis of Mind" (1953). Eccles and his co-workers from all around the world continued to work on the biophysical properties of motoneurons, of course, and to refine understanding of the ionic mechanisms underlying central excitation and inhibition many years after his NZL period. These contributions are summarized in his later books, "The Physiology of Nerve Cells" (Eccles, 1957) and