

Editorial

Brief History of Spinal Motor Functions

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At the time of ancient Greece, it was generally accepted that living organisms depended on *pneuma* which was regarded as principle potency of life. It was thought that *pneuma* entered the body through the respiratory system and was responsible for all functions of the nervous system including sensation, thoughts and movements. Although, ancient Greek philosophers processed several conceptions to explain the functions of sensory organs, they did not pay too much attention to movements due to the fact that they were considered as more primitive functions of the *pneuma*. **Aristotle** (384-322 B.C.) regarded the *pneuma* as a divine incorruptible element of the vital heat which is the foam-like natural principle of the breath. The *pneuma* is converted into vital *pneuma* in the heart and is transported to the muscles via the blood vessels to induce their contraction [1].

Galen (130-200) discovered that muscle contraction was initiated by spinal and cranial nerves, therefore the spinal cord had to be involved in movements. He also described that transection of the spinal cord resulted paralysis of muscles and loss of movements in the extremities below the level of injury. He regarded the *pneuma* like a fluid-like substance that flowed along the hard motor nerves to fill and carry the forces for contractions of the muscles [2]. In order to solve the inconsistencies between his anatomical results and Aristotle's conception, Galen established a new pathway for the *pneuma* which was called as spirit at that time. He introduced the animal spirit (*psychic pneuma*) which was produced from the vital spirit (*vital pneuma*) within the brain and then was carried to the muscles through the spinal cord and its nerves [3]. For more than one thousand years scientists believed that movements were initiated by *pneuma* or spirits. During the middle Ages the functions of the brain were localized into the ventricles. In accordance with religious notions, the *pneuma* was believed to be an immaterial soul which organized all functions of the body and was also confined into the ventricles. **Andreas Vesalius** (1514-1564) described that the inhaled air and the vital *pneuma* of the heart are converted into animal *pneuma* in the ventricles of the brain. The contraction of the brain forced this animal *pneuma* into the spinal cord which was regarded as network of tubules that distributed the *pneuma* between the fourth ventricle and spinal nerves which carried the *pneuma* into the muscles in order to perform their actions [4].

René Descartes (1596-1650) considered the animal spirit as the

physical components of the soul composed of very small particles which could be described by using mechanical terms. He thought that the corpuscles of the spirit were produced in the ventricles from the blood and were guided to the proper motor nerves by opening the valves on the wall of the ventricles. The movement of the animal spirit was controlled by movements of pineal gland where the soul exercised its function. The pineal gland as the place of *sensus communis* collected different sensory information which impressed the soul. The perception process caused slight movements of the pineal gland which was thought to hang within the ventricle. According to perceptible differences of the objects, the pineal gland was moved in different ways that altered the flow of the animal spirit and released it into different motor nerve to induce the appropriate movements [5].

About a hundred years later this reflex theory was further developed by **Thomas Willis** (1622-1675). He postulated that functions of the brain were dependent on cortex and not the ventricles. He thought that the animal spirits were made in the cortex of cerebrum and cerebellum by distillation of the blood and were distributed through the medulla oblongata and spinal cord towards the nerves. The sensory and motor processes of the nervous system were based on the movements of the animal spirits through small channels within the nerves. The movements of spirits were organized by an immortal and immaterial Rational Soul producing the internal representation of the images on the corpus callosum and corpus striatum and performing volitional acts to induce the proper motor events. He thought that the further distillation of the animal spirits at the end of the nerves was responsible for activation of muscles [6]. The significance of the spinal cord in organization of movements was systematically investigated by **Alexander Stuart** (1673-1742), **Jiri Prochaska** (1749-1820) and **Marshall Hall** (1790-1857) who proved that the spinal cord was able to initiate muscle contraction and reflexes in the absence of the brain. These results were inconsistent with Willis' theory which had regarded the animal spirits as key element for initiation of movements but confined their synthesis exclusively to the brain. This problem was solved by supposing that certain amount of the animal spirits - the so-called spinal spirits - could be produced within the substance of the spinal cord. At the same period of time **Luigi Galvani** (1737-1798) discovered that spinal nerves could conduct electricity in order to initiate reflexes and movements without the brain. Galvani thought that the spinal cord and its nerves possessed the ability to generate and conduct electricity in order to induce contraction of muscles.

By the end of the 18th century, the spinal cord was regarded as the center of locomotion which executed its involuntary motor function via spinal reflexes to contract groups of muscles responsible for a certain movements of the body.

In the nineteenth century several neuroscientists studied the spinal reflexes by irritation the part of the body or the nerve carrying the sensory information to the spinal cord. The elements of the spinal

reflex arcs in the spinal cord of frog were illustrated by **Michailovich Sechenov** (1830-1905) who considered the spinal cord as a biological machine producing involuntary automatic movements [7]. He showed that the spinal reflexes could be reinforced or inhibited through pathways coming from the brain. He extended the reflex theory from the spinal cord to the brain and thought that different functions of the brain including learning, memory or mental processes could be explained as complicated series of reflexes.

The details of the neuronal pathways underlying spinal reflexes were elucidated by **Sir Charles Sherrington** (1857-1952) and colleagues in a series of experiments at the beginning of the 20th century. Following natural stimulation of the skin or electrical stimulation of muscle afferents, they recorded changes in the length or the force of skeletal muscles. In these brilliant experiments Sherrington was able to elicit various reactions in the spinal cord that were classified as flexion-reflex, extension-reflex and crossed-extension-reflex. Sherrington also described that stimulation of the skin evoked series of rhythmic alternating contraction of flexor and extensor muscles constituting the stepping reflex [8]. He emphasized the significance of inhibition in the control of these spinal reflexes which might derive from inhibitory endings of afferent fibers or from descending cortical pathways. All excitatory and inhibitory effects are channeled towards the motoneurons called as “final common pathways” that could be selected in various combinations during different spinal reflexes.

The organization and cellular constituents of the spinal circuits involved in various spinal reflexes were further analyzed by **Sir John Carew Eccles** (1903-1997) and his co-workers. They studied neuronal pathways transmitting the recurrent inhibition of synergist motoneurons that had been demonstrated by Renshaw in 1941 [9]. Eccles concluded that motoneuron axon collaterals established cholinergic connections with spinal inhibitory neurons - were named after Renshaw by Eccles - which in turn, monosynaptically hypopolarized the spinal motoneurons via glycinergic neurotransmission [10]. By combining monosynaptic test reflex with direct intracellular recording from spinal motoneurons, they proved that in the inhibition between muscle afferents and spinal motoneurons was accomplished by a disynaptic pathway during stretch reflex. They identified Ia inhibitory spinal interneurons which conveyed the reciprocal inhibition between antagonists [11,12]. Sherrington had demonstrated earlier [13] that stimulation of receptors within a muscle could induce inhibition of motoneurons supplying the same muscle which was called later as “inverse myotatic reflex”. Eccles and colleagues showed that this inhibition was due to stimulation of Ib Golgi tendon organ afferents and was conveyed via disynaptic pathways [14]. The function of these interneurons in control of movements was demonstrated by Anders Lundberg, Elzbieta Jankowska and co-workers who investigated the convergence of inputs from primary afferents and descending pathways onto Ib inhibitory interneurons [15,16].

These studies demonstrated that spinal reflexes are flexible and function in state-dependent manner which allow the brain to select the pathways for the appropriate motor task. For example, when co-activation of antagonist muscles is required to stabilize the joints, the descending pathways may stimulate Renshaw cells which can decrease

the activity of Ia inhibitory cells via their monosynaptic connections.

Parallel with Eccle's work a new technique was developed which enable neuroscientists to record spike potentials directly from the somata of motoneurons with the help intracellular electrode [17,18]. The results of these studies showed that the contraction of skeletal muscle is sustained by repetitive firing of spinal motoneurons and the degree of contraction is proportional to the frequency of motoneuron discharge.

Although rhythm-generating capacity was assigned to the spinal cord by Sherrington in 1910, he was ambivalence concerning the significance of this central mechanism and believed that stepping rhythm was the results of sequential spinal reflexes induced by external stimuli from muscle receptors. Contrary this generally accepted opinion, **Thomas Graham Brown** (1882-1965) found that scratching and stepping could be elicited in completely de-afferented animals suggesting that rhythmic alternating contractions of muscles during these movements were initiated and controlled by intrinsic neuronal circuits of the spinal cord. In his earlier studies he had concluded that spinal scratching could be attributed to opposing paired centers within the spinal cord that control the contraction of flexor and extensor muscles, respectively [19,20]. Later, this “half-center” concept was extended to explain the control of stepping. He proposed that paired spinal networks composed of interneurons and motoneurons that organized the contraction flexor and extensor muscles during the swing and stance phases of the step. The flexor and extensor half-centers mutually inhibited each other and produced the appropriate locomotor rhythm which could be modulated by sensory inputs [21,22]. Brown showed that stepping movements could be elicited in the transected spinal cords after complete de-afferentation in decerebrated cats, rabbits and guinea-pig. The first experimental evidences about the existence of a spinal interneuronal network responsible for stepping were first provided by **Anders Lundberg** (1920-2009). After intravenous injection of DOPA, he revealed mutual reciprocal inhibition between spinal interneurons intercalated between flexion reflex afferent (FRA) and motoneurons [23]. Despite these convincing experimental and theoretical results, most scientists accepted that rhythm of stepping depends mainly on sensory inputs and could be adequately explained with chain reflex hypothesis until the end of 1960s. The existence of internal spinal rhythmic network was further confirmed by **Sten Grillner** (1941-) who showed that central activation of spinal cord induced clear rhythmic alternating activities in the spinal cats. At that time, the spinal circuits producing the appropriate patterns for rhythmic movements were commonly termed as central pattern generator (CPG) which was introduced by Wilson and Wyman in 1965 [24]. In the 1970s and the half center hypothesis was extended to explain different patterns of motoneuronal activity during normal and backward walking or climbing. Grillner supposed a group of interacting networks - called unit burst generators - that control the movements of single joints of each limb [25]. The movements of one limb derive from coordinated activity of these coupled unit CPGs that are controlled by supraspinal pathways.

On the other hand, it seemed that locomotion could not be explained as strictly alternating pattern of activity of flexor and extensor motoneurons. Usually a more delicate pattern was detected

and some motoneurons were active both in flexion and extension phases of the step. Nowadays, the original half-center network has been partitioned into multi-level models to explain these complex patterns of activity of motoneurons during locomotion [26-28]. In the last decades, a few populations of possible CPG interneurons have been identified by using electrophysiological techniques in the in vivo spinal cord of cats and in vitro isolated spinal cord of rodents [29-32]. Recently, genetic approaches using cell-specific transcription factors in transgenic mice proved to be very useful method in marking spinal rhythmically active interneurons [29,32,33].

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