ОБЗОРНЫЕ СТАТЬИ

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CEREBELLAR CONTRIBUTIONS TO LEARNING

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The cerebellum and its associated structures are involved in an associative sensorimotor task such as the Pavlovian conditioning reflexes. As early as 1929, investigations on the influence of cerebellar ablation on the defensive motor conditioned reflexes were carried out in the dog [45]. Further investigations in relation to this problem were carried out by various scientists [18, 36, 46, 47]. The influence of cerebellar ablation on the feeding conditioned reflexes was also investigated [27,28,33,35]. The cerebellar role in autonomic reactions and the spatial orientation of the animal was shown on the basis of the labyrinth, labyrinth-kinestetic and auditory stimuli by the method of conditioned reflexes [3] and the role of the cerebellum in accomplishment of some regulatory mechanisms pertaining to the functional status of the organs and tissues was also investigated.

According to many authors in cerebellar ablation there was a decrease or complete disappearance of positive conditioned reflexes and upon further rehabilitation, the possibility of elaboration of new positive conditioned reflexes was preserved. In decerebellated animals a sharp decline in the intensity of the inhibitory process was observed along with long lasting changes of the higher nervous activity according to the indices of the salivary methods in comparison to the results obtained by using methods of local motor conditioned reflexes.

Great attention is drawn towards the latter situation. Secretion of the salivary glands in addition to various methodical advantages allowed the consideration of the abnormalities in the conditioned reflex activity after cerebellar ablation because the animal cannot withstand severe violations of function like motility disorders. At the same time, the short term changes of local motor conditioned reflexes are not in accordance with the prolonged and severe disturbances in the motoric sphere of cerebellum ablated animals. There is a contradiction between the data on conditioned reflex activity and the general clinical picture of motor violations. Due to the above shortfall, a method of registration of movements in both the fore and hindlimbs was used in dogs. Such approach allowed to reproduce a more accurate dynamic reaction of the organism; for example in the study of peculiarities of the flow of effector generalization and the specialization of motor conditioned reflexes and, subsequently, to clarify the conditions under which the local conditioned reaction of the limbs was formulated. The elaborated inhibitory process is the basic mechanism of effector localization which seems to differ from that which provides receptor specialization and this process has a different localization [14]. The investigations conducted showed that the various components of the conditioned motor reaction are influenced in various degrees by the cerebellar ablation. The physical motor reaction of "reinforcing" the limb showed quick recovery, its tonical component weakened or disappeared in a fixed time. Maximal changes were observed in the proceed of inhibitory process – differential inhibition and mostly inhibition of the mechanisms providing effector specialization. The latter type of inhibition underwent prolonged irreversible changes reflecting adequately the picture of motor disturbance. Here, the specificity of cerebellar effect developed and the cerebellar deficit influenced all the areas of the central nervous system, finally causing spatial and time related changes of the subtle and interrelated activity of spinal cord motor neurons [12,13].

For this reason the cerebellum plays a great role in the posture and motor adjustment as well as in conditioning and motor learning. Evidence is now available showing that the cerebellum is necessary for the adaptation of the vestibulo-ocular reflex, for modification of the visual surroundings [22,34] and the classically conditioned eyelid response [39]. Most contemporary works on the neural mechanisms of conditioning used the nictitating membrane responses of the rabbit. In a large series of experiments on rabbits, it was shown that the cerebellum has a significant role in the elaboration of conditioned reflex of the nictitating membrane in response to visual or auditory stimuli. This reflex failed after the lesion of the cerebellar anterior interpositus nucleus and the hemispheral part of the lobule VI of the cerebellar cortex. The conditioning of the above mentioned reflex is also hindered by destruction of the rostral part of the medial accessory olive.. The reflex is strongly affected after the transection of the middle cerebellar peduncle in which the ponto-cerebellar fibers pass. In this model of conditioned reflex, the inferior olive takes part in the transmission of information related with the unconditioned reflex while the conditioned stimuli visual or auditory reach the cerebellum through the mossy fibers of the pontine nuclei [9,19,50]. In relation with the above, interest is devoted to the fact that using the above mentioned model, the activity of Purkinje cells of the hemispheral part of the lobule VI was registered during the elaboration of conditioned reflex of the nictitating membrane on stimulation by auditory signals. Both excitatory and inhibitory responses of Purkinje cells were observed which preceded the conditioned nictitating membrane reflex [42]. However, in the interpretation of the neuronal mechanisms of this type of reflex, it cannot be excluded that the cerebellar lesions may have interrupted only the motor expression of the association formed elsewhere in the brain.

The investigations conducted by Brogden and Gantt [4] had a special character. They reported that brain stimulation can be used as the unconditioned stimulus in a conditioning experiment. They used cerebellar stimulation to evoke limb movement. After pairing the cerebellar stimulation with an auditory stimulus, presentation of the conditional stimulus alone evoked movement of the limb. These stimulation experiments were early indicators that the associative processes for conditioning of a simple motor response may have a special relationship with the cerebellum rather than the cerebral cortex.

In another series of experiments, electrical stimulation of cerebellar nuclei in cats served as a conditioned signal for the conditioning of the food-procuring conditioned reflexes [15]. Parallelly the electrical activity of the cerebral cortex was registered, which gave the possibility to follow the changes in the cerebello-cortical transmission in the process of formation of a conditioned reflex activity. Low frequency electrical stimulation of the interpositus and dentate cerebebellar nuclei produced recruiting like responses (RR) in the cerebral cortex. It was shown that strengthening of the food-procuring conditioned reflex is accompanied by amplification and stabilization of the RR and the appearance of additional positive – negative potential complexes. In the process of extinction of the conditioned reflex, the picture of RR undergoes an opposite evolution: firstly the additional waves and later on the basic RR components disappear. The electrophysiological correlates of differential inhibition were revealed. A principal inhibitory character of cerebellar influence (interpositus or dentate nucleus) on the cerebral cortex through nonspecific thalamic nuclei and a predominantly activating nature of ascending cerebellar actions (fastigial nucleus) through the reticular formation of the midbrain was established during the above mentioned experiments. The synaptic mechanisms of the above noted effects were also investigated [16.17].

Physiological and pathophysiological data have documented the cerebellar involvement in motor control, the adjustment of muscular tone, coordination of the skilled voluntary movements and the regulation of posture and gait. The notion that the cerebellum is primarily or exclusively engaged in motor activity has become a classical topic. However, L. Orbeli [43] suggested a wider concept of cerebellar activity emphasizing the cerebellar modulation of the sensory and the autonomic functions. On analysis of the motor control by the cerebellum, it was divided functionally into the following regions - the lateral regions, modulating movement planning and programming and the intermediate and medial regions modulating the movement execution. The microstructural regularity of the cerebellar cortex and the anatomical convergence of the climbing fiber and mossy fiber input (via parallel fibers) on the Purkinje cells have been the basis of the theories of motor learning. It was shown that the microcomplexes, including the small cerebellar cortical zones and the cell groups of cerebellar and vestibular nuclei, serve as the basic functional modules of the cerebellum [20]. Concurrent activation of the climbing and parallel fibers forms a base for plastic changes of the synapses of parallel fibers on Purkinje cells [1,37]. All the above mentioned is the base for many phenomena seen in the cerebellar, motor adaptation, habituation, classical conditioning of the motor responses, timing, etc.

Long-term depression (LTD) of synaptic transmission at parallel fibers - Purkinje cell synapses in the cerebellum was the first established example of long lasting decrease in the synaptic efficiency of the central nervous system [21]. In experiments on rabbits it was shown that conjunctive stimulation at a low frequency (1-4 Hz) of parallel and climbing fibers impinging on the same Purkinje cell leads to LTD of synaptic transmission at the parallel fibers - Purkinje cell synapses and this change in synaptic efficiency is input specific, a crucial point for a mechanism involved in motor learning. In this model climbing fibers act as an external trainer, instructing the parallel fiber - Purkinje cell synapses to change their gain in such a way that the cerebellar cortical output becomes adapted to the appropriate motor command [32]. The climbing fibre action is mediated by an influx of Ca^{2+} into the dendrites, an event necessary to induce phosphorylation and, therefore, a reduced sensitivity of AMPA receptors. The climbing fibre synapse generates precisely timed Ca^{2+} transients in Purkinje dendrites. Strata and Rossi [48] provided novel suggestions about the involvement of climbing fibers in this process. In experiments where the Purkinje cells were deleted or the activity of cerebellar cortex was depressed, the terminal branches of climbing fibres retracted. In contrast when extra postsynaptic sites were available, there was a robust outgrowth of terminal arbors. They propose that climbing fibers might undergo dynamic adjustments in their anatomical features that enable them to participate in physiological plasticity. A very similar conclusion was made by de Zeeuw et al. [10], who on the basis of studies on the morphological characteristics of the inferior olive gromeruli proposed that the unique organization of the olivary neuropil microcircuitry is capable of functioning both in motor learning and motor timing. Thus, the olivocerebellar relationships appear as extremely important mechanism for cerebellar integration. In this model the inferior olive gives rise to all the climbing fibers innervating the Purkinje cells, while the Purkinje cells themselves are the sole source of the output signals of the cerebellar cortex that reach the central cerebellar and vestibular nuclei.

In the theories of motor learning, the cerebellum is assumed to be the storage site of the engram. Recent evidence shows that the cerebellum in addition to its mediation of simple motor responses has an important role in cognitive behavior. Since the cerebellum has an important role in motor learning, the changes in the Purkinje cell morphology may underlie the skills of acquisition. It was demonstrated that augmentation of synaptic contacts within the cerebellar cortex is associated with the motor skill learning and not with the motor activity alone. It was shown that trained animals had a significantly greater number of synapses on Purkinje cells [26]. It was also shown that skilled motor learning leads to a significantly greater dendritic arborization of the stellate cells of cerebellar cortex than their active controls [25]. These structural transformations are thought to represent qualitative and/or quantitative changes in the information processing which occurs in association with the changes in behavior.

The investigation of the cerebellar role in the ontogenesis of equilibrium behavior in young rats has shown that 10-day-old rats after cerebellectomy were unable to learn a given motor pattern, whereas 20 or 21-day-old rats, after cerebellectomy were able to learn the given motor pattern; however their skill was always lower than those of control animals trained from the same age. Cerebellectomy alters the ontogenesis of the equilibrium behavior which is more obvious if the operation is conducted in the early ages. It was shown that Purkinje cells which are polyinnervated by mossy fibers in a young rat, become monoinnervated (as in the adults) by the 15^{th} day after birth [6]. Therefore, when cerebellectomy is performed on 10-day-old rats the cerebellum is removed, while it is functionally immature, whereas in a 24-day-old animal the cerebellum was nearly mature. In both cases motor impairments during the days following cerebellectomy are similar. However the ontogenesis of the equilibrium behavior is quite different, since the animals cannot be trained efficiently when they are cerebellectomized in the immature stage, whereas training is efficient when cerebellectomy is performed when it is mature [2].

Since the role of cerebellum becomes critical by the 15^{th} day after birth special studies on this age period were conducted. Rats cerebellectomized on the 15^{th} day, which have not been trained before the operation, were unable to learn a given motor pattern. When trained before the operation, the animals learnt the motor pattern that was used to maintain their equilibrium, as well as the control animals [51]. It is important to note that the time of surgery appears to be a critical factor and this fact was proved on the basis of effects of cerebellar lesion performed at different developmental stages. Rats with a hemicerebellectomy, performed at adult hood or at weaning were compared behaviorally to rats with a similar lesion performed on the 1^{st} postnatal day. The age at which the animal received cerebellar lesions produced a significant difference with respect to the behavioral outcome in adult hood. Posture, locomotion and motor behavior were analyzed by a series of sensorimotor tests. Rats with a neonatal cerebellar lesions showed a slight extensor hypotonia contralateral to the lesion side and efficient locomotor activity , whereas the adult operated group had a severe extensor hypotonia ipsilateral to the lesioned side, hampered locomotion by a wide base and ataxia. Operated weanling rats displayed a symptomatology similar to that observed in adult operated, although less severe [41].

Therefore in addition to the age at which the operation was performed, it is necessary to observe the type of motor disorders [44]. However, it is necessary to note that the mice and rats with cerebellar damage caused by surgical ablations, gene mutations, X-ray irradiation during the developmental stages are impaired in maintaining posture and equilibrium. According to the majority of tests, even in animals with total cerebellectomy, postural sensorimotor learning is not abolished. Simple compensatory movements may be adopted [5]. The acquisition of simple sensorimotor skill occurring after a massive damage of the cerebellar cortex may be explained by the modulatory role of the central cerebellar nuclei during the learning processes [38]. A similar picture was documented in 15-day and 1-month-old puppies, after the removal of cerebellum in which the conditioning of the shaking off reflex was not hindered [11].

Phylogenetic evolution of cerebellum is strongly associated with the means of formation of the modes of functional and organic adaptation in animals to changes in environmental condition, which determines the form and character of the conditioned reflex activity of the animals of the given class and speices. By learning the special qualitative aspects of this switching on apparatus and the character of the formation of temporary bonds it is possible to comment about the three stages of development of conditioned reflex activity in the vertebrates [23,24].

The first stage is characterized by the fact that at the earliest levels of phylogenesis in the fish-like (lamprey) and various types of fishes the principal neurons apparatus for reflex switching on are the midbrain nervous structures and cerebellum. These systems are characterized by a concentration of afferent and efferent pathways of visual and auditory analyzers, which provide a high level of formation of temporary associations. At this level the temporary associations are very primitive and occur by summation reflexes.

The second stage of development starts at the amphibia, in which the system of afferent and efferent connections of primary visual and auditory centers shift from the cerebellum to the hemispheres of the forebrain. Cerebellum from the major adaptive organ converts into an organ with limited motor functions, not having relation in the formation of temporary connections. Simultaneously the forebrain hemispheral functional development by progressive speed occurs at the localization of the primary cortical cells at this transitory stage of development, when the cerebellum as a switching on apparatus loses its major significance in the formation of temporary associations, the other organ – hemisphere of the forebrain still do not acquire it, and the capability of the formation of temporary associations significantly decreases. It is due to the above reason that the conditional reflex activity of an amphibian is limited, which reflects their ecological peculiarities.

At the third stage the development of cerebral hemispheres (in birds) and then of the cerebral cortex (in mammals) forms the basic "switching on" system for the individually acquired forms of nervous activity and as a measure of the increasing significance of the cortex from the lower mammals to the higher. Conditioned reflex activity is formulated finally as a cortical activity, with all the specification of complex interrelation of the inhibitory and excitatory processes [23].

The cerebellar development has undergone great development in human. The significant enlargement of lateral cerebellum and dentate nucleus in humans provides a basis for the functional expansion of the cerebro-cerebellar system [29,30]. Reciprocal connections of the cerebellum to the prefrontal cortex have been shown and there is a possibility of modulation of human language functioning and the acquisition of mental skills, such as visual search procedures [31]. Special attention is attributed to a circuit involving the brain stem loop, formed by connections from the inferior olive to the dentate nucleus — to the red nucleus — to the inferior olive. Since the red nucleus receives a projection from cortical language areas, this neural loop may participate in language communication as well as motor function and may serve as a language - learning loop. A significant increase in the cerebellar blood flow during both mental counting and imaginary tennis training also tells about the involvement of cerebellum in humans in higher cognitive functions [8]. Cerebellar activation was more pronounced than the changes in any other region of brain and was interpreted as a specific activation of the cerebellum due to the mental activity taking place during imaging. The above features to some extent are confirmed by clinical observations during cerebellar disorders [7,29,40]. All the above mentioned findings point out the possible involvement of the human cerebellum in cognitive and language functions. It is still unknown how long the striking process of cerebellar functional modification lasted in the human evolution. Obviously the duration of this development is tremendously long, and may have been many millenium years. Historiography scrutinizes the great events of human history during a relatively short period and cannot reveal the fundamental aspects of changes. We always admire the accumulated wisdom of ages and the mighty considerations of ancient thinkers and their intrinsic intellectual ability to which the modern human being could add only some achievements in the technical domain and by this way our knowledge is furnished by new exploits.

Presently it is generally accepted, that the cerebellum with its relatively simple and regular synaptic organization has yielded much about its contribution to the brain function and its internal information processing. The representation of cerebellum as universal modulator and regulator of functional status and functional reflex arc is even accepted by many scientists [40]. The ontophylogenetic consideration of morphofunctional characteristics of the cerebellum shows its tremendous adaptation towards the problems of the organization of the neural activity of the phenotype the ecological living conditions and the evolutionary development. The morphofunctional modification is more significant in the cerebellum than in any other area of the brain. Depending on this, to a larger or smaller degree, various sides of the integrative activity of cerebellum arise. The cerebellum in an emergency contributes to quite different levels of learning and cognition by which broader limits of adaptation are demonstrated. Thus, vertebrate cerebella differ greatly in their external form, arrangement of the neurons of the cerebellar cortex and in prominence of their afferent, intrinsic and efferent connections [49]. Careful attention to these aspects of cerebellar activity will lead to a clearer understanding of the cerebellar mechanisms of learning.

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ՈՒՂԵՂԻԿԻ ԴԵՐԸ ՈՒՍՈՒՑՄԱՆ ԳՈՐԾԸՆԹԱՑՈՒՄ

Վ.Բ.Ֆանարջյան

Օժտված համեմատաբար պարզ և կանոնավոր սինապսային կազմակերպությամբ, ուղեղիկը նշանակալի ավանդ ունի ուղեղի ֆունկցիաներում և ներքին տեղեկության մշակման մեխանիզմներում: Նա կատարում է ռեֆլեկտորային աղեղների ֆունկցիոնալ վիճակի և ֆունկցիոնալ պատրաստության բազմաբնույթ փոխարկչի դեր:

Ուղեղիկի ձևաֆունկցիոնալ առանձնահատկությունների օնտոֆիլոգենետիկ դիտարկումը ցույց է տալիս նրա արտակարգ հարմարվածությունը ֆենոտիպի նյարդային կազմակերպության խնդիրներին, էվոլյուցիոն զարգացման մակարդակին, գոյության էկոլոգիական պայմաններին: Կախված այդ բանից, մեծ կամ փոքր չափով դրսևորվում են ուղեղիկի ինտեգրատիվ գործունեության տարբեր կողմերը, որն անհրաժեշտության դեպքում իր ավանդն է ներդնում ուսուցման և ճանաչման լիովին նոր ոլորտներում և նման ձևով ցուցադրում հարմարողականության ապշեցուցիչ լայն սահմաններ: Այդ բանով է բացատրվում այն փաստը, որ ողնաշարավորների տարբեր ներկայացուցիչների մոտ ուղեղիկը խիստ տարբերվում է իր արտաքին ձևով, կեղևային նեյրոնների տեղադրությամբ և կենտրոնաձիգ, ներքին ու արտատար կապերի առանձնահատկություններով:

ВКЛАД МОЗЖЕЧКА В ОБУЧЕНИЕ

В.В.Фанарджян

Мозжечок, обладая относительно простой и регулярной синаптической организацией, вносит существенный вклад в функции мозга и механизмы переработки его внутренней информации. Он выполняет роль универсального модулятора и регулятора функционального состояния и функциональной готовности рефлекторных дуг. Онтофилогенетическое рассмотрение морфофункциональных особенностей мозжечка свидетельствует о его чрезвычайной адаптированности к задачам организации нервной деятельности фенотипа, уровню его эволюционного развития, экологическим условиям обитания. В зависимости от этого в большей или меньшей степени проявляются различные стороны интегративной деятельности мозжечка, при необходимости вносящего свой вклад в совершенно новые сферы обучения и познания и, тем самым, демонстрирующего удивительно широкие пределы приспособляемости. Этим объясняется то обстоятельство, что мозжечок у различных позвоночных сильно отличается по своей внешней форме, расположению нейронов в коре мозжечка и основными особенностями своих афферентных, внутренних и эфферентных связей.

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