

The Red Nucleus: Past, Present, and Future

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ABSTRACT

The purpose of this review is to consider the regression of the magnocellular red nucleus and the progression of the parvocellular red nucleus.

The red nucleus (RN) can be divided into two histologically distinct structures: the parvocellular red nucleus (RNp) and the magnocellular red nucleus (RNm). Literature indicates that the origin of the RN can be attributed to the advent of limbs, or limb-like structures, in lower vertebrates. Research has shown that RNm and its primary efferent pathway, the rubrospinal tract, comprise most of the red nuclei related structures from early vertebrates through the mammals.

Imaging of the modern human brain displays a dominance of the RNp with marked regression of the RNm, at least related to size. The relatively large development of the RNp has been accompanied by uncertainty regarding its function in the humans. © *Neuroanatomy*. 2010; 9: 1–3.

Key words [red nucleus] [rubrospinal tract] [magnocellular] [parvocellular] [limbs]

The Red Nucleus

Vertebrate development has resulted in a diverse set of locomotion patterns. It has been postulated that modern motor movements of higher vertebrates are fundamentally derived from the swimming pattern present in aquatic chordates. When vertebrates became terrestrial, it is probable that the lateral paired fins of their aquatic predecessors became objects of locomotion in the air or on the ground [1]. Locomotion using limbs led to a dedicated descending pathway by which the central nervous system (CNS) could initiate movement. Examination of the red nucleus' role in limb movement requires an understanding of the structure's cytoarchitecture.

The structure of the red nucleus has changed considerably during mammalian development. Staining techniques used on many different species have shown that neurons of the RN fall into three general categories: small, medium, and large. Padel et. al [2] reported that in most animals leading up to mammals, the largest cells are generally found at the caudal pole, while in the middle and rostral parts of the nucleus, populations of medium-sized and small cells appear. The data fit the accepted idea of RNm composing the large-celled caudal portion of the red nucleus and RNp making up the smaller rostral area.

Studies of the mammalian red nucleus demonstrate that larger cells are found in RNm, whereas medium and small cells are typically found in RNp [3]. The volume of the nucleus taken up by these parts becomes

reversed over the course of time and across species. In reptiles and birds the nucleus is composed almost entirely of large cells [4]. This large-celled RNm is the most likely source of the contralateral projections of the rubrospinal tract prominent in early vertebrates [1]. Yet as the rubrospinal tract has regressed in primates so has the histological presence of RNm. The number of large cells in the RN seems to diminish progressively as one passes from carnivores to baboons to anthropoids to man [2]. Morphological studies in humans show an increased development of the RNp - enough that RNm and RNp are completely independent of each other in humans [5].

In lower vertebrates, telencephalospinal pathways are absent and reticulospinal pathways constitute the most primitive descending tracts involved in motor control [6]. Therefore, it is not surprising that primitive vertebrates do not exhibit a rubrospinal tract of any note [7]. Edwards [8] discussed the likelihood of tracts from the forebrain and brainstem, specifically the corticospinal and rubrospinal pathways, evoking limb movement in vertebrates. It was postulated that the emergence of limbs brought about a parallel development of control systems to coordinate limb movement, in this case the RNm and rubrospinal pathway.

Although the RN can be differentiated in some fishes and limbless reptiles, a rubrospinal tract has so far been demonstrated only in rays which use their pectoral fins for locomotion [1]. The fins of the ray are likely precursors to the limbs of terrestrial vertebrates [7]. Rubrospinal tracts are also absent in boid snakes and sharks who use

axial movements for locomotion rather than limbs [9]. Such data further implicates RNm and the corresponding rubrospinal tract in limb movement.

The rubrospinal pathway and its cell bodies in RNm have progressively declined from lower mammals to primates [4]. Some researchers note that the RNm, initially involved in the automatic execution of learned motor skills, has been progressively replaced by the pyramidal system [1]. Rubrospinal tract regression in bipedal primates has been suggested to be linked to the loss of locomotor function in the upper limb [7].

Massion [7] tested the hypothesis that linked rubrospinal tract regression to the acquisition of a bipedal stance by comparing rubrospinal neurons in the baboon to those of the bipedal gibbon. Massion believed that the rubrospinal cell population of the RNm controlling the lower limbs of apes would maintain its numbers with the upright stance. Data indicated otherwise, showing that the number of rubrospinal cells innervating lumbar segments of the spinal cord is reduced in gibbons. The degeneration of the rubrospinal tract in the gibbon is therefore not restricted to the cervical region and the data discount the theory of rubrospinal regression with acquisition of the bipedal stance.

Expansion of the pyramidal tract in primates has paralleled the regression of RNm [3]. One study has shown that axons from both the rubrospinal and pyramidal tracts end on the same segmental interneurons and propriospinal neurons [10]. An experiment involving lesions of the pyramidal tract in monkeys demonstrated a remarkable change in RNm organization in order to compensate for corticospinal tract loss to upper limb muscles [11]. It is therefore likely that RNm capability of output reorganization associated with pyramidal tract lesions demonstrates its role as a backup motor pathway to the dominant corticospinal pathway of primates.

Haines [12] indicates that relatively few rubrospinal axons have been shown to extend below the cervical enlargement of the human spinal cord. Clinical findings indicate that the human rubrospinal system exerts its control mainly over the upper extremity and has little influence over the lower extremity. The data strengthen the argument that RNm and its corresponding rubrospinal tract, with increasing dominance of the pyramidal tract, have shrunk to influence upper limb control only.

The RNm and the rubrospinal pathway are a simple, but comprehensive motor unit in lower vertebrates lacking a corticospinal tract [6]. Without a pyramidal tract it is likely that afferents to the RNm come mainly from the cerebral cortex in early vertebrates [4]. As the RNm diminishes, it would likely follow that afferents to it also change. Electrophysiological observation of the RNm in monkeys has shown that input to the RNm from motor cortex is much less significant than the input from the cerebellum [13].

It is clear that projections to and from the RNm have changed from early vertebrates through primates. While RNm influences all limb movements in lower vertebrates, it appears delegated to upper limb control in primates.

From both an anatomical and functional perspective the rubrospinal pathway appears to be ceding to the corticospinal tract as the primary motor pathway in bipeds – perhaps at least partially explaining the size decrease in RNm.

In consideration of the RNp, Donkelaar [1] correlated levels of connectivity of the RN in terrestrial vertebrates to development of the cerebellum. A primitive level of RN organization is present in amphibians with only one cerebellar nucleus and no evidence of a rubro-olivary projection. Limbed reptiles demonstrate a more advanced level of organization with lateral and medial cerebellar nuclei showing projections to the RN. The study also found evidence of the first indication of a RNp in the discovery of a rubro-olivary projection in quadrupedal reptiles. In mammals, such as the North American possum, data showed two cerebellar nuclei projecting contralaterally to the RN: the interposed nucleus to its magnocellular part and the lateral (dentate) nucleus to its parvocellular part. It was concluded that the relatively simple rubrospinal tract of lower vertebrates, such as amphibians and reptiles, along with the absence of a corticospinal tract, was consistent with the more stereotyped behavior of these vertebrates. The greater repertoire of movements in mammals involves a more complex circuitry, including a higher complexity level of the RN and an increased development of the pyramidal tract.

What little is known about the human RNp has been inferred mostly from research done on monkeys. Structural and functional dominance of the RNp over the RNm division has become more apparent with the development of independent arm-hand movements and a large increase in the size of the lateral cerebellum with its connections to the cerebral cortex [15]. In monkeys, it appears as though most cortical input to the RN is restricted to the RNp [3]. Since RNm receives much of the cortical input in lower vertebrates, it is likely that RNm and RNp have changed functional roles in primates.

Though input from the cerebral cortex is a major mode of activation in the primate RNp, excitatory input from the dentate nucleus must also be considered. The RNp is involved in a loop between the inferior olive and the cerebellum [15]. Given the cerebellum's association with motor activity, the RNp's connection to the inferior olive would indicate its likely role as a motor structure as well.

Recent neurological imaging suggests that the cerebellum may be more involved in sensory processing than originally thought [16]. With evidence proposing the involvement of the cerebellar system with sensory stimulation, Liu et. al [17] did research to examine possible sensory activation of RN. Functional MRI was used to assess activation levels of the dentate nucleus and RN when human subjects performed a pair of passive and active tactile finger tasks. Results showed that the RN, along with the dentate nucleus, was activated by purely sensory stimuli even in the absence of the opportunity to coordinate finger movements. With the relative size of the RNp in humans and its correlation with the dentate nucleus, it is likely that most of the activation in the dentate nucleus would come from the RNp. In light of this

data and the recent recognition of sensory capabilities of the cerebellum, it appears that while the exact function of the RNp remains unknown it may be involved in some form of sensory processing.

Conclusion

The RN of early vertebrates is a functionally and anatomically different structure than that of the human RN. RNm of lower vertebrates is part of a dominant motor pathway controlling movement of limbs. Anatomically, RNm is the prevailing portion of the RN in these creatures. The telencephalization process and the development of the neocerebellum in primates has brought about a higher level of motor circuitry, possibly causing the pyramidal tract to flourish and the RN to reorganize.

The RNm of primates has been shown experimentally to be involved with lesser degrees of motor control for muscles of the upper limb than the dominant corticospinal tract. RNm appears to be a backup to the corticospinal tract, with both pathways sharing synapse locations in the spinal cord. The yield of motor control to the pyramidal tract, together with decreasing cortical

input, may explain the decrease in size of RNm from lower mammals to humans.

RNp has expanded in humans due to its prevailing projections from the dentate nucleus and the prefrontal, temporal, and occipital cortices [15]. RNm's consistency with rigid and stereotyped motor behavior in vertebrates impeded its prosperity; meanwhile the RNp has endured the development of higher motor centers in the brain like the dentate nucleus. Data show that RNp has increasingly integrated itself with higher levels of function, for instance sensorimotor processing. Further research of the cerebellar nuclei in terms of sensory function, their correlations with the RNp, and the inferior olive will undoubtedly raise questions about our understanding of the RN.

Data on the activation of the human RNp during tactile discrimination tasks point to it as a sensory structure. Current consideration acknowledges that these findings are consistent with the idea of the RN being related to voluntary limb movements. New studies also raise the question of whether activation patterns in the RNp may be secondary to the movement itself, and might be more related to the use of the arm, hand, and fingers in tactile sensory data acquisition [17]. Additional experiments will be necessary to clarify the role of RNp.

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