様式３

論　文　内　容　の　要　旨

氏　名　（　原　聡史　）	
論文題名	Formation of Interstitial Branches Selectively Within the Red Nucleus by Deep Cerebellar Nuclei-Derived Commissural Axons During Target Recognition （発達期小脳核ニューロン軸索の正中交差後における赤核認識に関する研究）

論文内容の要旨

The correct wiring of the nervous system depends upon a series of guidance events during neural development that gradually establish the proper pattern of neuronal connectivity. Over the past several decades, studies of neural circuit formation have focused extensively on the cellular and molecular mechanisms of axon pathfinding. Commissural axons, for example, have been particularly well documented for investigating the mechanisms and logic of axon guidance. However, the process of target recognition by these axons after midline crossing has received less attention, so the mechanisms that underlie this critical event remain poorly characterized to date. In this study, in order to examine how commissural axons recognize their specific targets on the contralateral side, I analyzed in detail the behavior of post-crossing commissural axons derived from the deep cerebellar nuclei (DCN) in the developing mouse cerebellum. For this, a cell-type-specific genetic labeling approach in vivo was employed to selectively visualize individual DCN axons during the time when these axons project to the red nucleus (RN) in the brainstem, one of the well-characterized targets of DCN axons. Here, it was shown that when DCN axons initially entered the RN at its caudal end, these axons continued to grow rostrally through the RN without showing noticeable morphological signs of axon branching. Interestingly, after a delay, DCN axons started forming interstitial branches from the portion of the axon shaft selectively within the RN. Because commissural axons acquire responsiveness to several guidance cues when they cross the midline, I further addressed whether midline crossing is a prerequisite for reception of target-derived cues normally received by post-crossing DCN axons. For this, a *Robo3* knockdown strategy was used to prevent midline crossing by DCN axons in vivo. It was shown that DCN axons were still capable of forming interstitial branches within the RN even in the absence of midline crossing. These results therefore suggest that the mechanism of RN recognition by DCN axons involves a delayed interstitial branching, and that these axons possess an intrinsic ability to respond to the target-derived cues irrespective of midline crossing.

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論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

申請者は、交連ニューロン軸索の正中交差後の標的認識過程を実際の脳の中のin vivoで捉えることで、特異的な神経回路網が形成されるメカニズムを明らかにする研究を行った。本研究では、マウス小脳核由来の交連ニューロンを選択的に可視化させ、その標的である脳幹の赤核を特異的にラベルすることで、小脳核ニューロン軸索の赤核領域における挙動をin vivoで解析した。その結果、小脳核ニューロン軸索は正中交差後の対側脳幹において、赤核に侵入した当初は形態学的な変化を示さないが、その軸索先端が赤核を通過した後で、赤核内部の軸索区画から選択的に側枝を形成させることが明らかとなった。さらに、小脳核ニューロン軸索の赤核認識には軸索正中交差が必ずしも必要ではないことも示された。以上の結果は、交連ニューロン軸索の標的認識過程の詳細を明らかにしたものであり、その標的認識機構が軸索正中交差とは無関係に交連ニューロンに内在していることを示唆している。これらは新規性の高い重要な成果であり、本研究は学位の授与に値するものと考えられる。