40.O4

Insular Cortical Grafts: Factors Affecting the Recovery of Learning

Federico Bermúdez-Rattoni, Martha Escobar, Ricardo Tapia and Marcia Hiriart

Instituto de Fisiología Celular, UNAM P.O. Box 70-600 Mexico, D.F. 04510, Mexico

The insular cortex (IC), or visceral neocortex, is known to be involved in aversive related learning and memory processes. The IC receives taste and visceral information from the thalamus and sends direct projections to the nucleus of the tractus solitarius (the first-order relay for visceral information). The IC also has connections with limbic structures, including the amygdala and medial prefrontal cortex. Lesions of the IC region in adult rats impair the acquisition and retention of conditioned taste aversion (CTA). Recent findings showing that N-methyl-D-aspartate lesions of the IC disrupt the acquisition of inhibitory (passive) avoidance tasks, indicate that the IC is also involved in exteronociceptive-based learning.

Our research has focused on the recovery of the acquisition of conditioned taste aversion and inhibitory avoidance learning task, by fetal brain grafts in IC-lesioned animals. In a first series of experiments, we have shown that cortical brain grafts produced a significant recovery in the ability to learn in IC-lesioned animals. The recovery induced by fetal brain grafts was related to the origin of the graft tissue used. That is, animals that received homotopic (IC), but not occipital cortical tissue recovered the capability to learn the CTA task. The IC-grafts produced a significant recovery in the ability to learn at 60 days post-graft. Biochemical analyses revealed that IC fetal grafts released GABA, ACh and glutamate in response to K^+ depolarization. In contrast, occipital grafts released GABA and glutamate, but not ACh. Results with a horseradish peroxidase (HRP) retrograde tracing technique revealed that cortical, but not brainstem, grafts established connections with amygdala and ventromedial nucleus of the thalamus. In further experiments, rats with lesions of IC showing disrupted taste aversions received neocortical grafts and were retrained at 15, 30, 45 and 60 days after transplantation. The behavioral results showed almost complete functional recovery at 60 days, slight recovery at 30 and 45 days and a poor recovery at 15 days post-graft. HRP histochemistry revealed that at 15 days there were no HRP labeled cells in the ventromedial nucleus or in the amygdala. At 30, 45 and 60 days post-graft, there were an increasing number of HRP labeled cells, almost as many as those seen in the controls, in the thalamus and the amygdala. The behavioral recovery was correlated with increased acetylcholinesterase activity, detected histochemically, and with morphological maturation, revealed by Golgi staining. The possibility that neurotrophic factors alone may be involved in the functional recovery is unlikely, because it is necessary to wait at least 30 days to see any recuperation. Therefore, such findings suggest that if neurotrophic factors are involved, they need to be associated with cortical homotopic grafts and/or with some time dependent factor essential for producing functional recovery. These series of experiments also suggest that cortical grafts' maturation and/or ACh activity may play a role in graft-mediated behavioral recovery.

Recently, we have evaluated the role of nerve growth factor (NGF) in the recovery of CTA and inhibitory avoidance induced by cortical grafts. The behavioral results showed that IC, but not occipital, grafts plus NGF promote recovery of learning at 15 days post-graft, 30 days earlier than without NGF. Biochemical analyses showed that ChAT activity in the homotopic grafts+NGF was similar to the intact control animals. The IC-grafts with vehicle showed a significantly reduced ChAT activity

when compared with IC-grafts+NGF or controls. In other experiments, it was observed that at 130 days post-graft the functional recovery in animals that received IC with or without NGF was similar to controls. These findings suggest that NGF, when associated specifically with homotopical grafts, notably accelerates the recovery of learning abilities in IC-lesioned rats.

In our model, the application of NGF alone did not produce significant functional recovery at any of the post-graft times tested. Further, the best functional recovery was seen when the NGF was associated with homotopical, cortical grafts but not with heterotopical occipital grafts. These behavioral results appear to be related to the integration and maturity of the grafted tissue. Preliminary results using the Golgi staining technique indicate that the cortical grafts with NGF showed more neuronal maturation compared to the cortical grafts with vehicle alone. Therefore, as mentioned, if neurotrophic factors are involved, they need to be associated with cortical, homotopical grafts and/or certain factors essential for producing recovery of learning abilities in insular cortical lesioned animals.

Supported by UNAM-DGPA 20-46-89 and CONACYT 0178-N9107.