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## Function of Agrin for synapse formation in adult neurogenesis.

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► **To cite this version:**

Angelique Desoeuvre, Tiveron Marie-Catherine, Camille Boutin, Beurrier Corinne, Cremer Harold. Function of Agrin for synapse formation in adult neurogenesis.. 9ème colloque - Société des Neurosciences, May 2009, Bordeaux, France. . hal-04772256

**HAL Id: hal-04772256**

**<https://hal.science/hal-04772256v1>**

Submitted on 7 Nov 2024

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### INTRODUCTION

While Agrin is a heparan sulfate proteoglycan, it is also a cell surface receptor that binds to the cell surface receptor tyrosine kinase (RTK). This is a cell surface receptor that is involved in the regulation of the cytoskeleton.

In addition to its proteoglycan properties, Agrin is a cell surface receptor that binds to the cell surface receptor tyrosine kinase (RTK). This is a cell surface receptor that is involved in the regulation of the cytoskeleton.

Since then, Agrin has been shown to be involved in the regulation of the cytoskeleton and in the formation of the synapse. Agrin is a cell surface receptor that binds to the cell surface receptor tyrosine kinase (RTK). This is a cell surface receptor that is involved in the regulation of the cytoskeleton.

### Expression of Agrin and a3NakATPase in the OB

Agrin is highly expressed in the RMG and OB (b). Co-localizing with a3NakATPase demonstrates its specific expression in neuronal precursors (c). In the OB, Agrin is expressed in a subpopulation of neuronal precursors (d). In contrast, a3NakATPase is expressed in all precursors in the OB (e). Agrin is also expressed in the complex fiber layer (f) and is not expressed in the granule cell layer (g). However, after RTK activation, Agrin is phosphorylated in the granule, internal and ponsular layers of the OB (d-f), suggesting that Agrin is a receptor for Agrin in the OB.

### Agrin does not influence neuronal migration in vitro

To investigate a possible role of Agrin in the migration of neuronal precursors, we used the embryonic culture system. Neurons obtained from the E18.5 lateral ganglionic eminence (LGE) of WT (a) and Agrin-deficient (b) embryos were cultured for 72 hours in medium. Under these conditions, neuronal precursors migrate from the LGE to the OB. The number of individual cells and the mean migration distance (in  $\mu\text{m}$ ) were measured. The results show that Agrin does not play a role in the proliferation nor in the migration of neuronal precursors in the OBs.

### Transplantation of Agrin deficient neuronal precursors into WT hosts

Directly examining the function of Agrin in OB neurogenesis in vivo has proved to be difficult because Agrin knockout mice die at birth. To investigate the function of Agrin in adult neurogenesis, we transplanted neuronal precursors from Agrin-deficient mice into the OB of wild-type mice. The cells were cultured in vitro for 72 hours and then grafted into the OB of wild-type mice. At varying time points after grafting, animals were sacrificed and GFP-expressing cells were analyzed.

### Cell transplantation: 10 days later

Class 1: Differentiated mature neurons with dendritic arborization (a). Class 2: Cells with no dendritic arborization (b). Class 3: Cells with no dendritic arborization (c). Class 4: Dead neurons (d).

10 days post-grafting, neural precursors of transplanted brain were processed to observe the behavior of grafted neuronal precursors in the RMG (a and b), and in the OB (c and d). No difference between control cells and Agrin-deficient cells was observed in the OB in all of their migration, distribution or individual morphology in the OB, confirming that Agrin does not play a role in migration/infiltration of neuronal precursors. In both locations, the majority of cells showed no more immature morphology (e and f). However, detailed analysis and classification of the different population stages of transplanted neurons in the granule and ponsular layers showed that more control than Agrin-deficient cells showed immature morphology (g-h).

### 17 days after transplantation

Class 1: Differentiated mature neurons with dendritic arborization (a). Class 2: Cells with no dendritic arborization (b). Class 3: Cells with no dendritic arborization (c). Class 4: Dead neurons (d).

17 days post-grafting most of the control cells have reached the OB and integrated the OB circuitry. Multiple dendrites and dendritic spines can be observed on ponsular and granule neurons (e and f, quantification in g-h). In contrast, the majority of Agrin-deficient neuronal precursors appears unable to integrate in OB (e and f). The surviving precursors present an average morphology, with the degree of maturation (h and i), showing that Agrin is necessary for the integration of transplanted mature granule neurons in OB.

### 2 months after transplantation

In our cases, control and Agrin-deficient tissue vesicles neurogenic for up to two months. Even in the OB, Agrin mutant cells in the OB do not show signs of synaptogenesis (i-c), while control cells show multiple synapses (d-f).

**CONCLUSIONS**

We suggest that the neuronal receptor for Agrin in OB is the alpha5 subunit of the NMDA receptor.

Based on the present system we conclude that Agrin does not play a role in the migration nor in the proliferation of neuronal precursors. This is confirmed by OB transplantation experiments, showing that Agrin-deficient cells integrate normally in the RMG and OB.

Thus, these analyses show that Agrin is necessary for integration of new neurons in the adult olfactory bulb, probably via the induction/maturation of new synapses.