**CHRONIC CITALOPRAM TREATMENT COUNTERACTS KAINDIC ACID-INDUCED INCREASE IN PSA-NCAM-EXPRESSING CELLS AND AVOIDS MIGRATION IN ADULT MOUSE HIPPOCAMPUS**

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**BACKGROUND**

Selective serotonin reuptake inhibitor citalopram is widely used antidepressant compound in the treatment of depression, recently it has been introduced also as possible treatment option in epilepsy. The mechanisms through which antidepressants alter neuronal excitability and modify seizure threshold remains largely unknown. The expression levels and patterns of molecules involved in the neuronal structural plasticity of neural tissue, like cell adhesion molecules are thought to be involved in the pathogenesis of epilepsy (Pilgrim & Stutin, 2002). The neuronal cell adhesion molecules NCAM (Edelmann, 1986) plays a major role in cell-cell and cell to extracellular matrix interactions (Crusell & Kruh, 2000). Adhesive properties of NCAM can be regulated through the addition of polysialic acid (PSA) which creates plasticity in the positioning and movements of the cells and/or their processes (Brunes & Reth, 2001). PSA-NCAM is strongly expressed during neural development and generally down-regulated in the adult, however, it remains prominent in some brain areas that exhibit physiological plasticity (Seki & Ami, 1995), like dentate gyrus (DG) of the hippocampus, where generation of new neurons persists throughout whole life. It has been demonstrated that the number of young neurons, expressing PSA-NCAM and their distribution in the DG is altered after repeated seizures, which indicate increased migration of newly generated as well as plastic changes of preexisting neural cells occur in response to recurrent generalized seizures (Sato et al., 2003). Accumulation of immature neurons in the DG depicts an increased risk of establishment of aberrant synaptic contacts and formation of aberrant neural networks within hippocampal formation eventually affecting hippocampal functioning (Scarfman et al., 2002) which may be relevant in the pathogenesis of epilepsy.

Whether antidepressants could avoid alterations in the expression of PSA-NCAM following seizures is not known. To study the possible role of adhesion systems as underlying mechanisms mediating the effects of antidepressants in epilepsy we used systemic kaicnic acid (KA) administration, which is widely used animal model of human temporal lobe epilepsy (Buckmaster & Dudek 1997).

**AIMS OF THE STUDY**

In this study we focused mainly on two research questions:

1. Whether or not the chronic pretreatment with selective serotonin reuptake inhibitor citalopram could decrease seizure severity induced by systemic kainic acid administration and secondly, whether the chronic citalopram administration could avoid alterations in the number and positioning of young, not fully matured PSA-NCAM expressing cells in the adult mice dentate gyrus.

2. To determine alterations in the positioning of the PSA-NCAM-positive cells within the GCL of the DG, the proportion of cells located in the proliferative zone as well as cells located outside the proliferative zone were counted and the proportion of cells outside the proliferative zone was calculated. Also the mean distance (μm) of PSA-NCAM-immunoreactive cells from proliferative zone was measured.

**MATERIALS AND METHODS**

3 month old male Balb/c mice were pretreated with citalopram (a generous gift of H. Lundbeck A/S, Copenhagen, Denmark, 10 mg/kg, i.p) for 7 days after that the single dose of kainic acid (KA) (Buckmaster & Dudek 1997). Administration of KA caused seizures in all animals. Evaluation of the severity of seizures was performed using the following scale from 0 to 5 as described previously (Racine, 1972). Mean score of seizures for vehicle treated or citalopram treated animals received KA, was calculated in different time points (every 15th minute) and data was represented as mean seizure score for each experimental group. Administration of citalopram was continued once a day for additional 21 days following KA administration. After that animals were transcardially perfused and brain coronal sections (40 μm) were prepared and immunohistochemical staining for PSA-NCAM and signal was visualized using the ABC system and diaminobenzidine as chromogen. The total number of PSA-NCAM-positive immunoreactive cells was calculated as described previously (Heidmets et al., 2000). To evaluate the localization of PSA-NCAM-positive cells within the GCL of mice dentate gyrus, light microscope images were taken using a digital camera. Every PSA-NCAM-positive cell located on the proliferative zone was marked with a point. In order to present a mathematical model of the proliferative zone's edge, an orthogonal regression was defined based on the coordinates of these points. Then, every migrated cell within the GCL was marked with a point as well as the coordinates of those points were used to draw another orthogonal regression. To characterize the migration of cells the distance between the two lines was measured and expressed in micrometers.

**RESULTS**

Effect of citalopram administration on kainic acid induced seizures

Administration of KA caused seizures in all animals. Evaluation of the severity of seizures revealed, that the mean score of seizures during the two hour period was significantly higher in kainic acid animals compared to group in which citalopram was administered (Fig.1). The authors do not have a commercial or other association that might pose a conflict of interest.

**REFERENCES**

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**C O N C L U S I O N S**

Our results demonstrate that chronic citalopram administration decreases seizure severity induced by kainic acid, counteracts in the expression of PSA-NCAM and avoids abnormal positioning of these PSA-NCAM-immunoreactive cells in the granule cell layer of the adult mouse hippocampus. Thus, an antidepressant-induced decrease in the PSA-NCAM could be one possible mechanism by which antidepressants alleviate KA-induced alterations in brain plasticity.

**G R A N T  S U P P O R T**

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