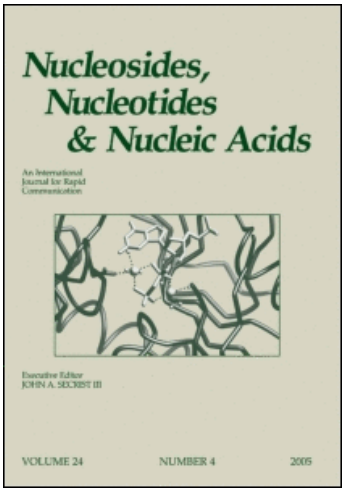

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REGIONAL CHANGES IN RAT BRAIN ADENOSINE A1 RECEPTORS FOLLOWING SEIZURES

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Abstract. Generalized seizures induced a widespread upregulation of adenosine A1 receptors linked to G proteins in the rat brain. Changes in receptor density were more pronounced in structures mediating seizure activity and were age-dependent.

In the central nervous system, adenosine has been shown to be a major regulator of neuronal activity in convulsive disorders, mainly via the A1 receptor subtype. Experimental seizures raise the cerebral level of adenosine in animals and adenosine and its derivatives act as protective agents against seizures in rodents. In a previous work, we were able to show that generalized seizures induced by an acute administration of bicuculline in rats lead to an age-dependent upregulation of adenosine A1 receptors measured in isolated cerebral membranes[1]. However, no information was available concerning the regional changes in the receptor density.

In the present study, the effects of bicuculline-induced seizures were investigated by quantitative autoradiography of central adenosine A1 receptors in developing rats and in adults. Six animals at each stage of postnatal development (5, 15, 25 days and adults) received a single i.p. injection of either saline or bicuculline. They were sacrificed by decapitation 30 min after drug administration and brain sections were incubated for 90 min at room temperature in the presence of 5nM [^{3}H]cyclohexyladenosine (CHA), a potent A1 receptor agonist. Non specific binding was assessed with 20 µM cold CHA. Seizures induced a widespread increase in adenosine A1 receptors, significant in 41 out of the 45 brain regions studied, with a marked enhancement of CHA binding in structures that mediate seizure activity, such as substantia nigra,

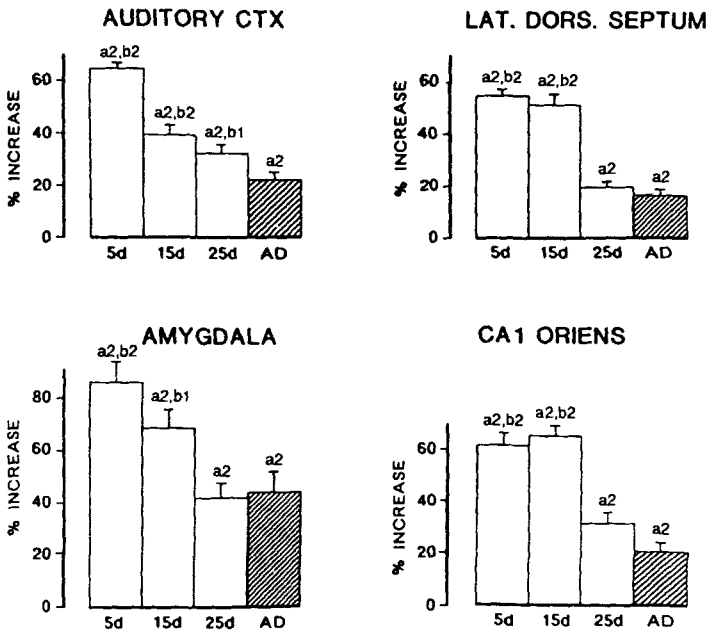

FIGURE 1 : Age-dependent changes in [^{3}H]CHA specific binding following seizures in four brain structures (percent of variation from control). Significant difference from control : a2 ($p<0.01$) and from changes in adults : b1 ($p<0.05$), b2 ($p<0.01$).

septum, amygdala, the different layers of hippocampus, as well as in cerebral cortices (Figure 1). Moreover, the addition of 2.10^{-5} M Gpp(NH)p, a GTP analogue, into the incubation medium reduced [^{3}H]CHA binding in a similar manner whether animals were given bicuculline or saline, suggesting that increased CHA binding sites are also linked to G proteins and are functional receptors.

In conclusion, our study supports the hypothesis that seizures result in facilitating the inhibitory action of adenosine on cell firing by increasing the density of A1 receptors, especially in discrete brain structures concerned in the generation or in the propagation of seizure activity. Such a phenomenon would be more pronounced in developing- than in mature brain.

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