

## GABA MECHANISMS IN AUDIOGENIC SEIZURES STUDIED USING HERPES VIRUS AND LENTIVIRUS MEDIATED GENE TRANSFER

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Viral gene transfer was used to alter expression of GABA receptor  $\alpha$ -1 subunits and GAD production to study effects on the audiogenic seizure (AGS) model for epilepsy. Long–Evans rats acoustically primed with a 125-dB 10-kHz tone at postnatal day (PND) 18 were tested at PND 32 for AGS using 125 dB white noise stimulation. Seizure resistant animals were not exposed to a priming signal. Subjects ( $n = 8$ ) were AGS-tested 2 and 3 days before surgery on PND 50–100, and again 2, 3, and 4 days after surgery; additional post-testing to 30 days was added for lentivirus animals to study the effects of long-term expression. The central nucleus of the inferior colliculus was bilaterally injected with replication-defective herpes virus (ICP4-;  $2 \times 10^6$  plaque forming units) encoding GAD<sub>65</sub> and GABA<sub>A</sub>  $\alpha$ -1 mix subunits in the sense; lentivirus vectors (multiply attenuated, replication defective and self-inactivating) encoded GABA<sub>A</sub>  $\alpha$ -1 sense or GAD<sub>65</sub> sense. Seizure-prone rats injected with GAD<sub>65</sub> and GABA<sub>A</sub>  $\alpha$ -1 mix sense herpes viral vector showed a significant reduction in the incidence of overall clonus,  $t(7)=2.865$ ,  $p<0.05$ . There was also a marginal decrease in the incidence of wild running between all pre-tests and post-test 3:  $t(7) = 2.268$ ,  $p=0.058$ , as well as significant decreases between each post-test and Post-test 3. In lentivirus GABA<sub>A</sub> -1 sense AGS animals, there was no significant change in the latencies to wild running. However, the latency to clonus increased significantly from pre-testing to post-test 2 ( $F=10.528$ ,  $p<0.05$ ), post-test 4 ( $F=15.180$ ,  $p<0.05$ ), and post-test 5 ( $F=19.042$ ,  $p<0.05$ ), as compared with seizure control rats. Studies using GAD<sub>65</sub> sense lentivirus suggest that this vector is also highly effective in decreasing the incidence of seizure behaviors. There was a significant increase in the latency to wild running from pre-test 1 and 2 to post-tests 5, 8, and 9 ( $p=0.05$ ), as compared to a control group. The latency to clonus also showed a significant increase for post-test 4 ( $p<0.01$ ) and post-test 6 ( $p<0.05$ ). The incidence of AGS seizure behaviors also decreased in rats injected with GAD<sub>65</sub> sense Lentivirus; Chi-square analysis for the incidence of wild running showed a significant decrease,  $\chi^2=4.122$ ,  $p<0.05$ . Overall incidence of clonus also significantly decreased,  $\chi^2=7.811$ ,  $p<0.005$ . Staining for lacZ (B-galactosidase expression) showed typical collicular fusiform and stellate cells. These results show that manipulation of the production of GABA through the GAD enzyme or the GABA<sub>A</sub> receptor subunits using viral constructs can directly alter epilepsy, a finding that may potentially have future clinical implications. Supported by NSF SES-0244632 and EPSCoR EPS-0132573/NIH BRIN 8-P0RR16461A (JRC).