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CNSC-01. GABAERGIC NEURON-TO-GLIOMA SYNAPSES IN DIFFUSE MIDLINE GLIOMAS

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High-grade gliomas include clinically and molecularly distinct subtypes that stratify by anatomical location into diffuse midline gliomas (DMG) such as diffuse intrinsic pontine glioma (DIPG) and hemispheric high-grade gliomas. Neuronal activity drives high-grade glioma progression both through paracrine signaling and direct neuron-to-glioma synapses. Glutamatergic, AMPA receptor-dependent synapses between neurons and malignant glioma cells have been demonstrated in both pediatric and adult high-grade gliomas, but neuron-to-glioma synapses mediated by other neurotransmitters remain largely unexplored. Using whole-cell patch clamp electrophysiology, in vivo optogenetics and patient-derived glioma xenograft models, we have now identified functional, tumor-promoting GABAergic neuron-to-glioma synapses mediated by $GABA_A$ receptors in DMGs. GABAergic input has a depolarizing effect on DMG cells due to NKCC1 expression and consequently elevated intracellular chloride concentration in DMG tumor cells. As membrane depolarization increases glioma proliferation, we find that the activity of GABAergic interneurons promotes DMG proliferation in vivo. Increasing GABA signaling with the benzodiazepine lorazepam – a positive allosteric modulator of $GABA_A$ receptors commonly administered to children with DMG for nausea or anxiety - increases $GABA_A$ receptor conductance and increases glioma proliferation in orthotopic xenograft models of DMG. Conversely, levetiracetam, an anti-epileptic drug that attenuates GABAergic neuron-to-glioma synaptic currents, reduces glioma proliferation in patient-derived DMG xenografts and extends survival of mice bearing DMG xenografts. Concordant with gene expression patterns of $GABA_A$ receptor subunit genes across subtypes of glioma, depolarizing GABAergic currents were not found in hemispheric high-grade gliomas. Accordingly, neither lorazepam nor levetiracetam influenced the growth rate of hemispheric high-grade glioma patient-derived xenograft models. Retrospective real-world clinical data are consistent with these conclusions and should be replicated in future prospective clinical studies. Taken together, these findings uncover GABAergic synaptic communication between GABAergic interneurons and DMG cells, underscoring a tumor subtype-specific mechanism of brain cancer neurophysiology with important potential implications for commonly used drugs in this disease context.