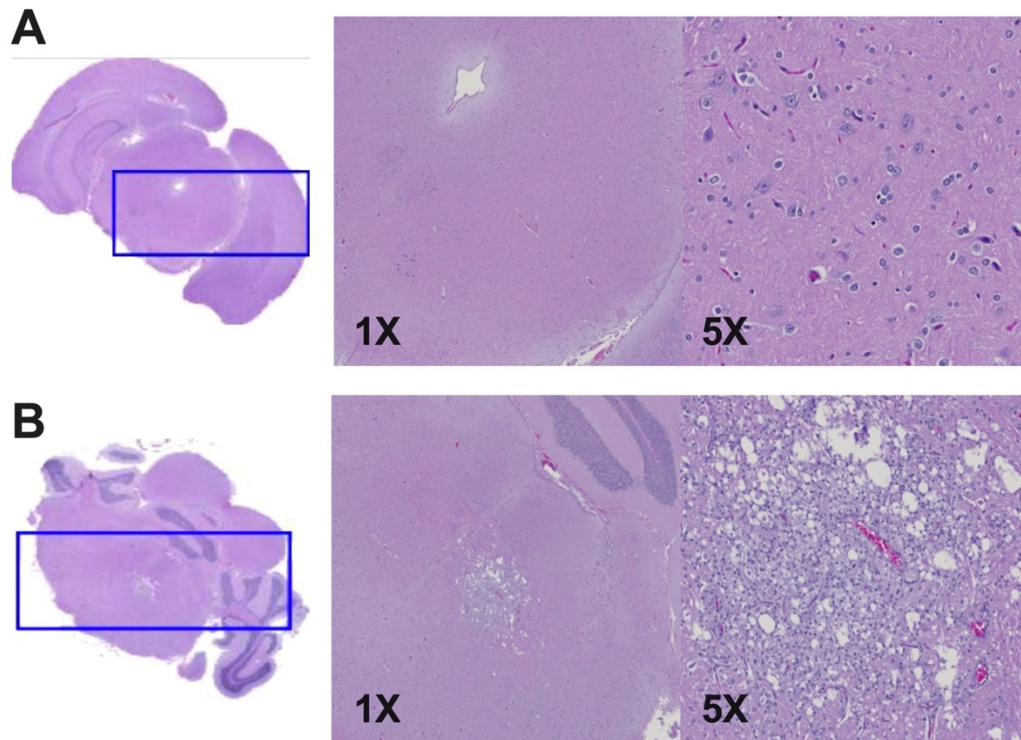
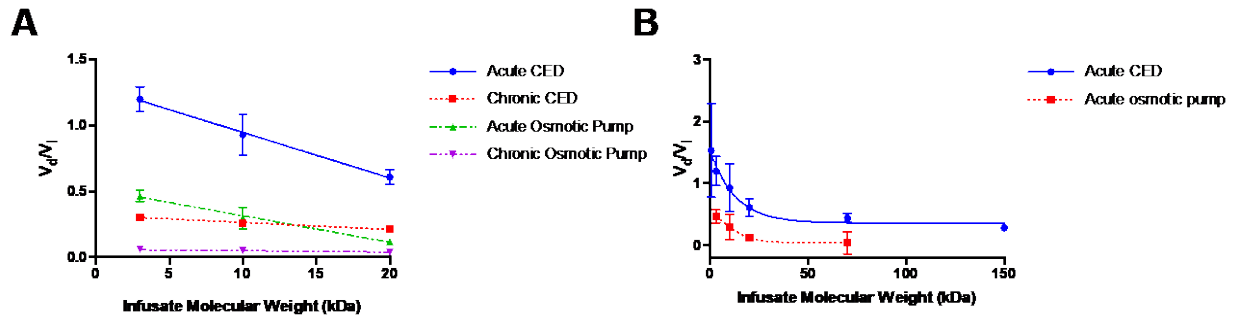


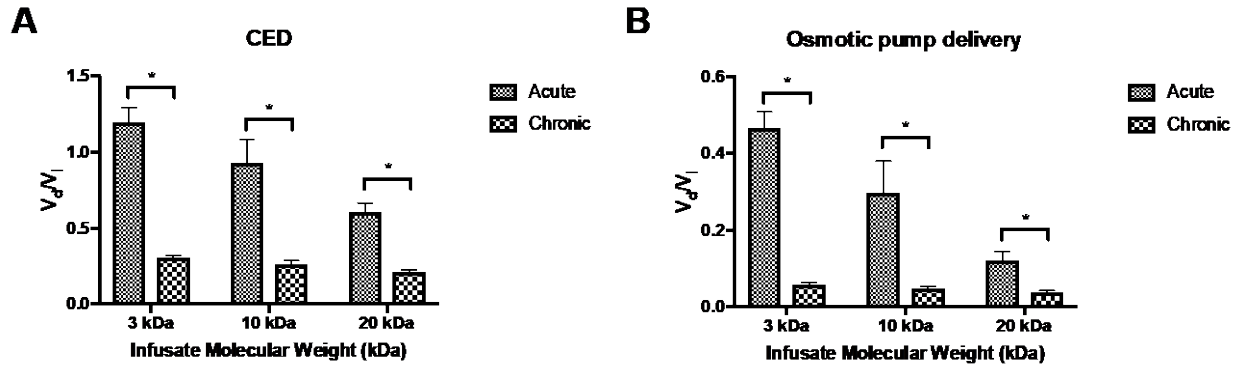
Supplementary Figures



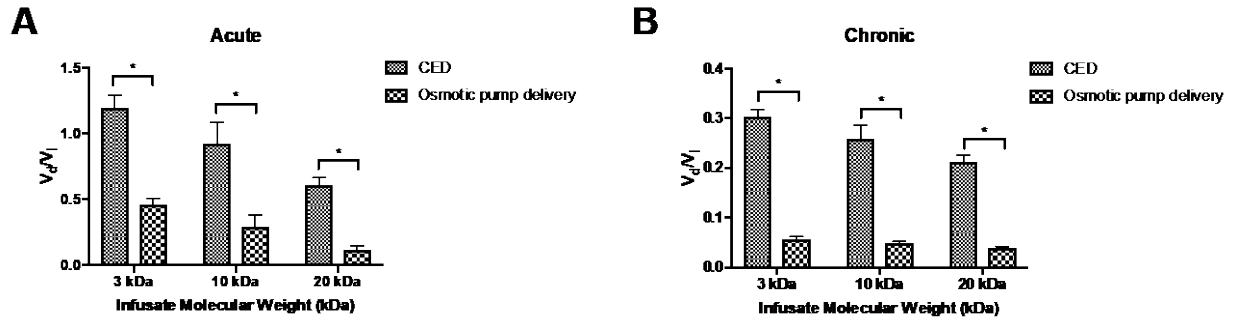
Supplementary Figure 1. Representative hematoxylin and eosin-stained coronal 20 µm sections of rat brainstem immediately following infusions of sterile isotonic saline via CED **A)** after a single 90 µL injection over 1.5 hours with the absence of gross or microscopic histological changes, and **B)** after five daily 90 µL injections over 1.5 hours each depicting small cavitory lesions along the cannula tract.



Supplementary Figure 2. Inversely proportional relationship between infusate MW and standardized volume of distribution to infusion volume (V_d/V_i) in multiple settings. **A)** In the 3-20 kDa range, this relationship was linear (R^2 , 0.99 in all settings). **B)** For acute CED and osmotic pump over a broader range, 570 Da up to 150 kDa, this relationship was better modeled by an exponential model (R^2 , 0.91 and 0.94 respectively). All data points were obtained from n=3 brainstems and presented as mean \pm SD.



Supplementary Figure 3. Comparison of V_d/V_i after acute versus chronic infusion by **A)** CED and **B)** osmotic pump delivery grouped by infusate MW. All data points represented as mean \pm SD, and were obtained from n=3 brainstems. Statistical significance determined by means of student's t-test and $P < 0.05$ marked by (*).



Supplementary Figure 4. Comparison of V_d/V_i after CED versus osmotic pump delivery infusion in either **A)** an acute setting (1.5 hrs CED, 24 hrs osmotic pump delivery) or **B)** a chronic setting (1.5 hrs CED daily for five days, five continuous days for osmotic pump delivery) grouped by infusate MW. All data points represented as mean \pm SD, and were obtained from n=3 brainstems. Statistical significance determined by means of student's t-test and $P < 0.05$ marked by (*).