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Low blood glucose precipitates spike-and-wave discharge activities in a mouse model of epilepsy

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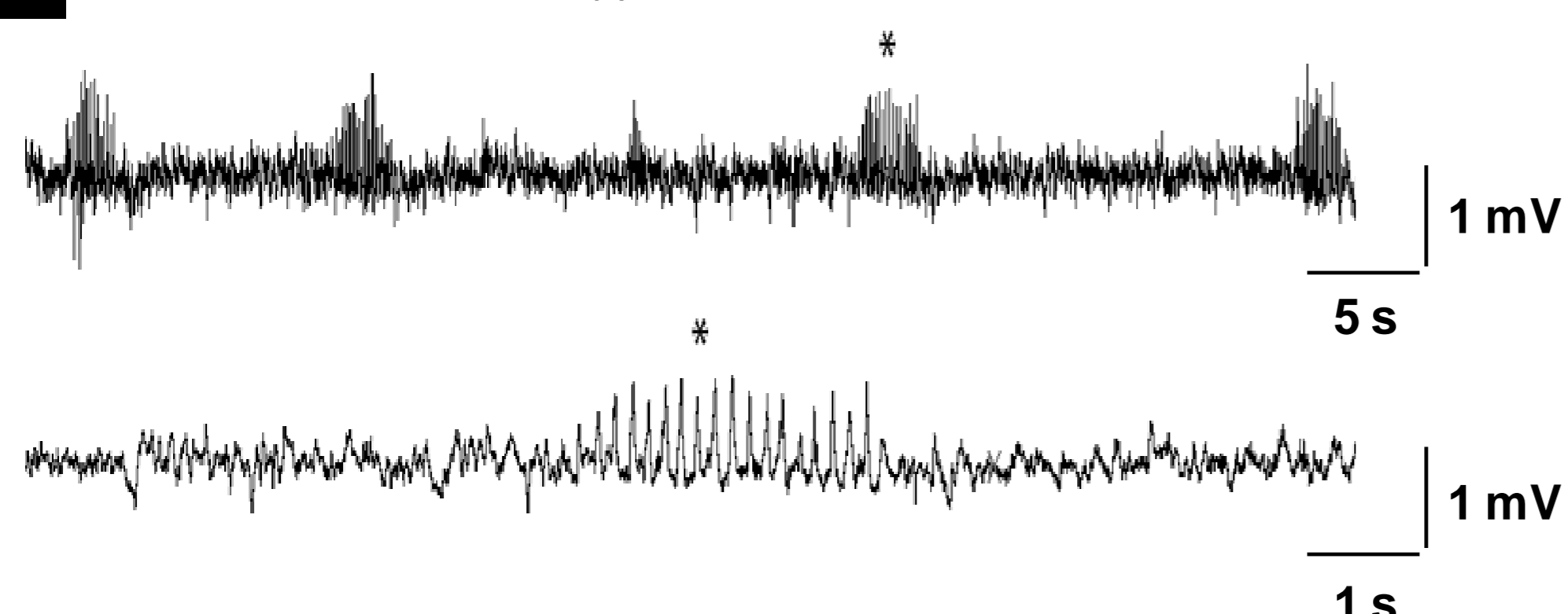
Purpose

Absence seizures are defined as unprovoked behavioural arrest associated with generalized spike and wave discharge (SWD) on EEGs. Absence epilepsies have a largely genetic aetiology but it is well known that environmental effects such as decreased vigilance and voluntary hyperventilation may induce seizures. However, we still don't have a complete understanding of all the environmental precipitants. Low glucose in general has not been considered an environmental factor but the manifestation of absence epilepsy in patients with brain glucose transporter deficiencies has raised this possibility. Here we investigate if lowering blood glucose can precipitate SWD activity in a animal model of absence epilepsy.

Methods

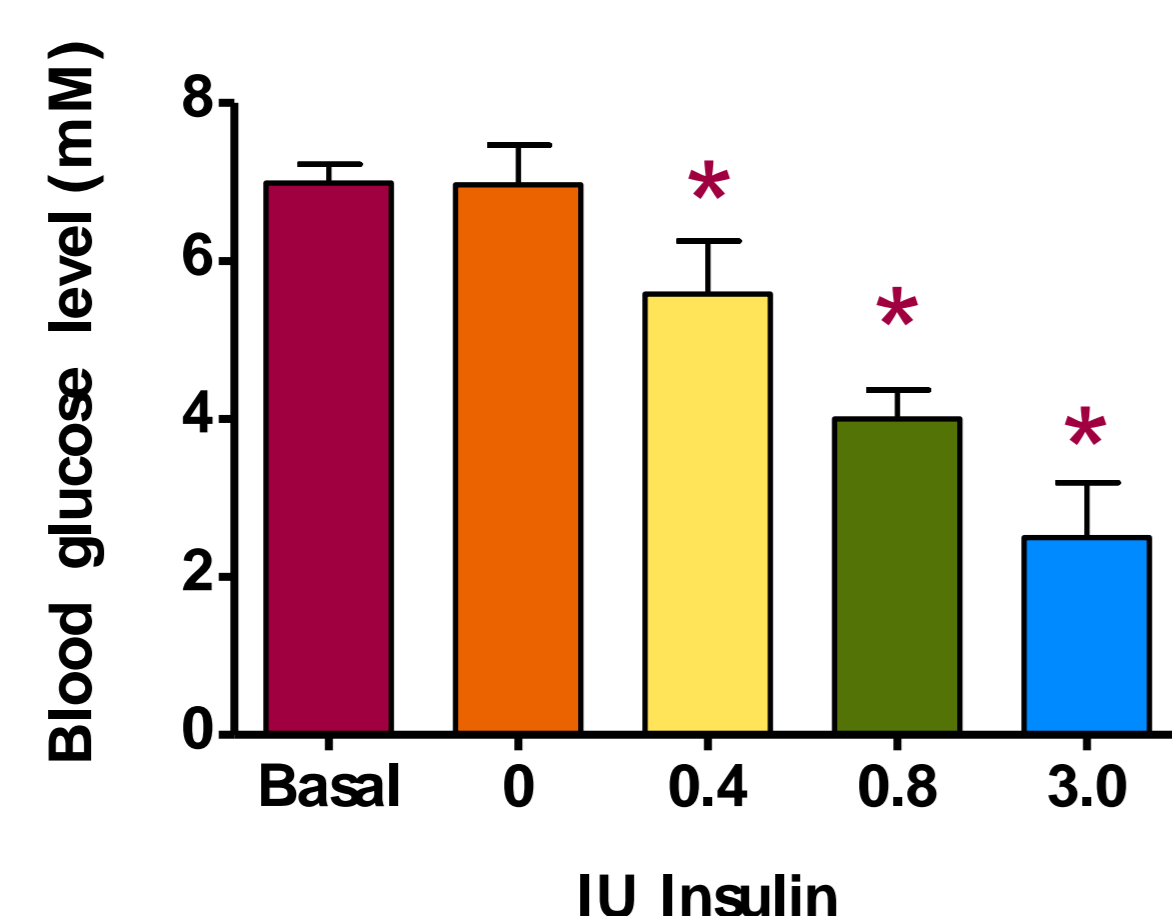
A mouse model of absence epilepsy based on the knock-in of the human GABA_Aγ2 (R43Q) mutation was used. Hypoglycaemic states were modelled using IP insulin injection at various doses and by overnight fasting (~16 hours). Blood glucose level were measured from mixed peripheral blood. EEGs were recorded to quantify change in SWD activity before and during hypoglycaemia. Statistical comparisons were made using paired T-Test.

i SWDs in GABA_Aγ2 (R43Q) model



A mouse model of absence epilepsy based on a human mutation. Lower trace displays the expanded SWD.

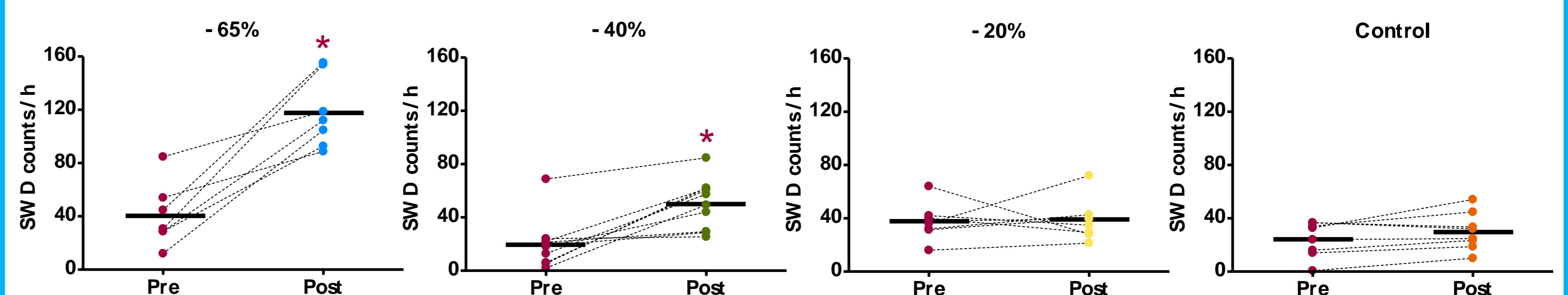
ii Modelling hypoglycaemia with insulin



Dose dependent impact of insulin on blood glucose levels.

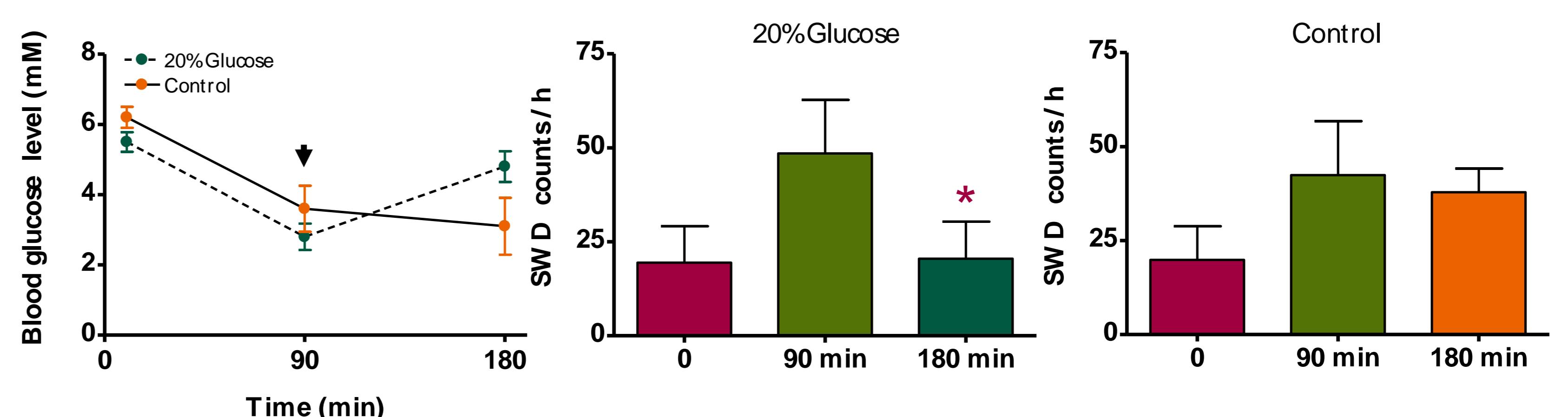
Results

1 Impact of insulin on SWD activity



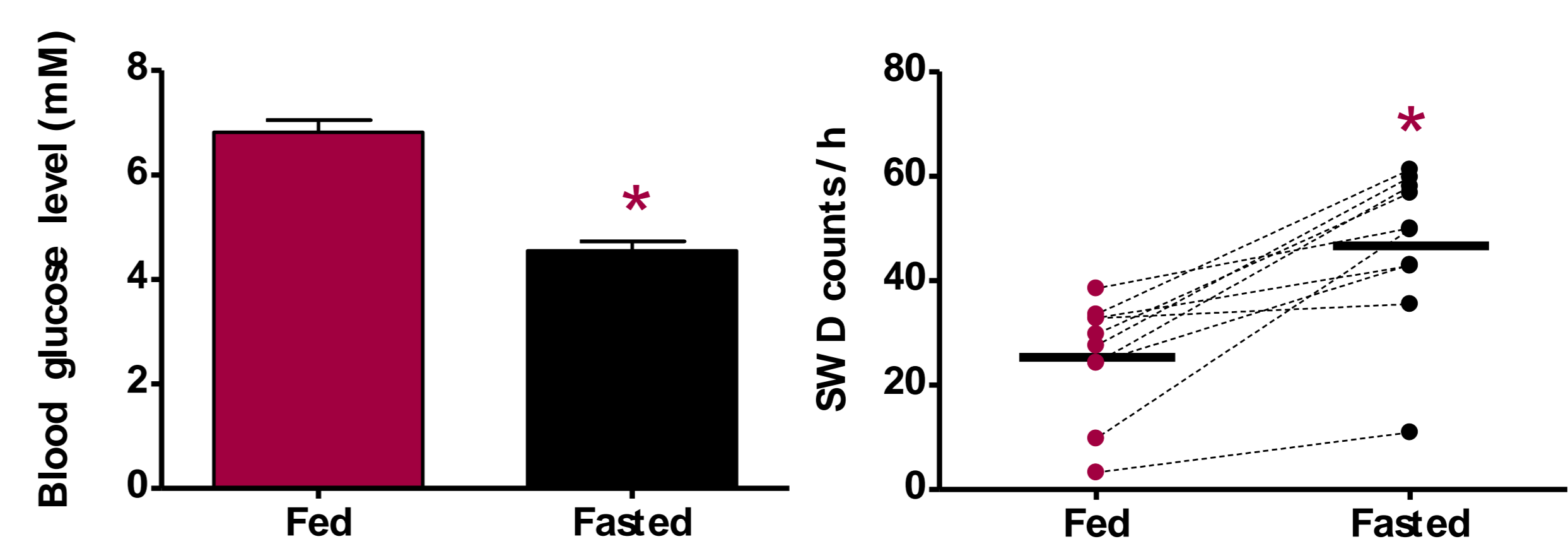
A ~40% reductions in blood glucose leads to a doubling of SWD counts. The impact on SWDs is greater at lower blood glucose levels.

2 Glucose injection reverses the impact of insulin



Glucose injection reverses the impact of insulin suggesting low blood glucose and not insulin *per se* as the cause of increased SWD activity.

3 Overnight fasting doubles SWD counts



Overnight fasting leads to a ~35% reduction in blood glucose and a doubling of SWD counts. This suggests that physiological plausible fluctuation in blood glucose could act as an 'environmental risk factor' in absence epilepsy.

Conclusion

This study highlights a highly reproducible, immediate, reversible and dose dependent impact of low blood glucose on SWD expression in the animal model of absence epilepsy. We also showed that overnight fasting can reduce blood glucose levels sufficiently to precipitate SWD activity. Our findings suggest that low blood glucose needs to be considered as a potential environmental risk factor in absence epilepsy motivating further clinical studies into this phenomenon.