



## COMMENTARY

## Neurological Changes in Hypoglycemia

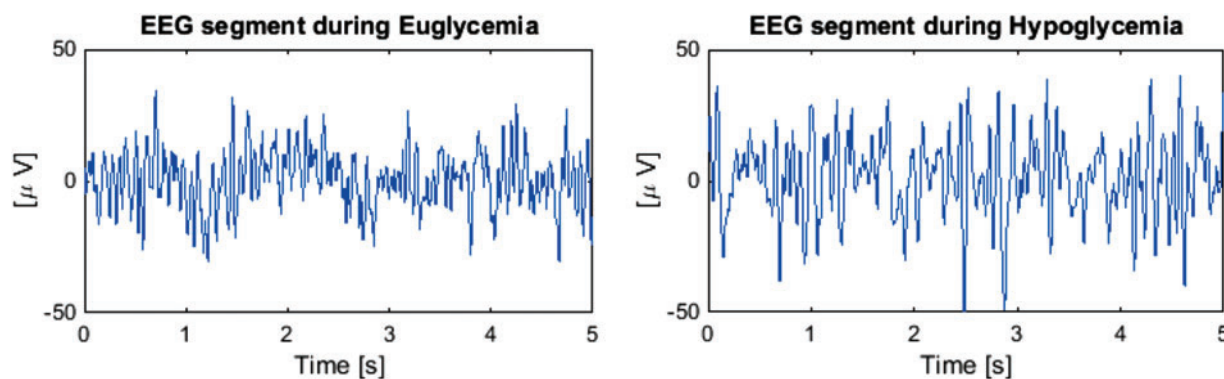
AU2 ▶ AU1 ▶ Maria Rubega and Giovanni Sparacino

**AU3 ▶** GLUCOSE IS THE MAJOR source of energy for the human brain and its regulation is critical for brain physiology.<sup>1</sup> Glucose is required for both neurotransmitter synthesis and several glucose-metabolizing enzymes control cellular survival, but the largest amount of glucose is consumed for neural computation. Furthermore, the brain increases its glucose consumption upon activation.<sup>2</sup> In particular, in adult brain, neurons have the highest energy demand and the blood–brain barrier that separates the circulating blood from the brain extracellular fluid is highly selective and permeable for glucose. Thus, glucose is an energy source that is not replaceable for the brain. The huge range of physiological, hormonal, symptomatic, and cognitive responses triggered by the fall in blood glucose is mainly caused by elevated levels of epinephrine, but epinephrine responses to hypoglycemia might become impaired in type 1 diabetes (T1D),<sup>3</sup> leading to hypoglycemia unawareness. So, T1D patients can develop a high risk to fall in asymptomatic hypoglycemia, further reducing the efficacy of the counter-regulatory responses to future hypoglycemia.<sup>4</sup> In the literature, the alterations of cerebral functioning consequent to the hypoglycemic condition have been investigated through both qualitative and quantitative analyses of the electroencephalogram (EEG) signal. The first studies aimed to see whether cognitive dysfunction was mirrored by altered EEG activity during hypoglycemia date back to more than 60 years ago. Specifically, abnormal EEG activity defined as slow potentials was observed in ref.<sup>5</sup> and distorted EEG waves with higher amplitude during hypoglycemia were reported in ref.<sup>6</sup> In the past decades, the increase in the power of low frequency bands, that is, delta and theta frequency range, during hypoglycemia in T1D patients was assessed in many studies in the literature.<sup>7–10</sup> In Figure 1, it is even qualitatively observable by visual inspection that the EEG signal in the hypoglycemic condition originates from a process of higher amplitudes in the low frequency bands and reveals greater regularity. More subtle changes induced by hypoglycemia, related to the altered complexity of the overall system, have been recently revealed by the use of nonlinear methods, that is, multiscale sample entropy and fractal analyses. Indeed, during hypoglycemia, the EEG signal results are more regular, more uniform, less complex than those of euglycemia.<sup>11,12</sup> Other studies exploited approaches resorting to multivariate analysis, that is, several EEG channel deri-

vations are considered at the same time. In particular, the functional reaction of the brain to hypoglycemia also showed a decrease in connectivity by computing the networks of directional effects of one EEG recording channel over another.<sup>13,14</sup> Specifically in ref.<sup>14</sup> this decrease in the connectivity was seen in the path from the occipital lobes to the temporal and central lobes during hypoglycemia, most likely as a result of the alterations of mental and perceptual functions during this critical glycemic state. The demonstrated EEG abnormalities in the hypoglycemic pathological condition suggested a possible use of the brain as a biosensor to detect hypoglycemia in T1D through EEG monitoring by subcutaneous electrodes and real-time data processing by means of a multiparameter algorithm.<sup>15</sup> A research prototype device, able to measure the EEG signal by subcutaneous electrodes and then analyze and classify it in real time, has been proposed for the detection of hypoglycemia events<sup>16</sup>; however, this EEG-based hypoglycemia detection device still needs to be tested in a clinical setting.

So far, the notion that hypoglycemia affects EEG rhythms is well established,<sup>17–19</sup> but the adaptation of neurological function to hypoglycemia is open to discussion in both healthy and diabetic subjects. The article by Sejling and colleagues published in this issue of *Diabetes Technology & Therapeutics* assesses how hypoglycemia-associated changes are affected by an antecedent episode of hypoglycemia in T1D patients. Despite subtle differences seen in cognitive function and counter-regulatory hormonal response, the study of Sejling and colleagues affirms that hypoglycemia-associated EEG changes are not affected by an antecedent episode of hypoglycemia, in both hypoglycemia aware and unaware T1D patients. This hypothesizes that there is not an immediate adaptation of the brain to acute hypoglycemia. Sejling and colleagues underline that the effect of recurrent hypoglycemia on the brain seems controversial as reported in the literature. For instance, a single episode of mild antecedent hypoglycemia attenuated several aspects of cognitive dysfunctions during subsequent hypoglycemia in healthy subjects in ref.<sup>20</sup> whereas glycemic thresholds for hypoglycemic cognitive dysfunction did not seem to shift after antecedent hypoglycemia in ref.<sup>21</sup>

Moreover, Sejling and colleagues find an increase in theta, alpha, and alpha–theta amplitudes during hypoglycemia than during euglycemia, and these hypoglycemia-associated EEG



**FIG. 1.** Representative electroencephalogram (EEG) signal (C4-A1A2 derivation) measured in a hospitalized type 1 diabetes patient who underwent a hyperinsulinemic–hypoglycemic clamp: 5 s interval of signal during euglycemia (left panel) and hypoglycemia (right panel). Data taken from Rubega et al.<sup>14</sup>

changes do not differ between the two groups, that is, aware and unaware subjects, and the two experimental days. This seems not in line with the study in T1D made in ref<sup>22</sup> in which a single episode of hypoglycemia resulted in both high glycaemic thresholds for automatic and symptomatic responses to hypoglycemia and impaired physiological defense against this pathological state the next morning in T1D patients. Furthermore, an interesting finding reported in ref<sup>23</sup> showed an early and immediate reduction in vigilance and an early increase in EEG slow waves after even a slight lowering of blood glucose in severely hypoglycemia unaware patients than in aware patients.

In conclusion, although hypoglycemic events in patients affected by T1D were proved to be associated with measurable EEG changes, the level of adaptation of neurological function to hypoglycemia is still a debatable question. The study of Sejling and colleagues shed light on this problematic aspect, but there is room for further investigation, also using more sophisticated signal processing methodologies.

#### AU5 ► Author Disclosure Statement

No competing financial interests exist.

#### References

1. Mergenthaler P, Lindauer U, Dienel GA, Meisel A: Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci* 2013;36:587–597.
2. Sokoloff L: Energetics of functional activation in neural tissues. *Neurochem Res* 1999;24:321–329.
3. Briscoe VJ, Davis SN: Hypoglycemia in type 1 and type 2 diabetes: physiology pathophysiology and management. *Clin Diabetes* 2006;24:115–121.
4. Cryer PE: Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;350:2272–2279.
5. Fabrykant M, Pacella BL: Association of spontaneous hypoglycemia with hypocalcemia and electrocerebral dysfunction. *Arch Inter Med* 1948;81:184–202.
6. Ross IS, Loeser LH: Electroencephalographic findings in essential hypoglycemia. *Electroencephalogr Clin Neurophysiol* 1951;3:141–148.
7. Eeg-Olofsson O, Petersen I: Childhood diabetic neuropathy: a clinical and neurophysiological study. *Acta Paediatr* 1966;55:163–176.
8. Tsalikian E, Becker DJ, Crumrine PK, et al.: Electroencephalographic changes in diabetic ketosis in children with newly and previously diagnosed insulin-dependent diabetes mellitus. *J Pediatr* 1981;99:355–359.
9. Baskaran A, Milev R, McIntyre RS: A review of electroencephalographic changes in diabetes mellitus in relation to major depressive disorder. *Neuropsychiatr Dis Treat* 2013; 9:143–150.
10. Pramming S, Thorsteinsson B, Stigsby B, Binder C: Glycaemic threshold for changes in electroencephalograms during hypoglycaemia in patients with insulin dependent diabetes. *Br Med J (Clin Res Ed)* 1988;296:665–667.
11. Fabris C, Sparacino G, Sejling A-S, et al.: Hypoglycemia-related electroencephalogram changes assessed by multiscale entropy. *Diabetes Technol Ther* 2014;16:688–694.
12. Scarpa F, Rubega M, Zanon M, et al.: Hypoglycemia-induced eeg complexity changes in type 1 diabetes assessed by fractal analysis algorithm. *Biomed Signal Process Control*, 2017 (2nd revision under evaluation).
13. Cooray GK, Hyllienmark L, Brismar T: Decreased cortical connectivity and information flow in type 1 diabetes. *Clin Neurophysiol* 2011;122:1943–1950.
14. Rubega M, Sparacino G, Sejling AS, et al.: Hypoglycemia-induced decrease of eeg coherence in patients with type 1 diabetes. *Diabetes Technol Ther* 2016;18:178–184.
15. Elsborg R, Remvig L, Beck-Nielsen H, Juhl CB: Detecting hypoglycemia by using the brain as a biosensor. *InTech*, 2011.
16. Juhl CB, Højlund K, Elsborg R, et al.: Automated detection of hypoglycemia-induced eeg changes recorded by subcutaneous electrodes in subjects with type 1 diabetes—the brain as a biosensor. *Diabetes Res Clin Pract* 2010;88:22–28.
17. Hansen GL, Foli-Andersen P, Fredheim S, et al.: Hypoglycemia-associated eeg changes in prepubertal children with type 1 diabetes. *J Diabetes Sci Technol* 2016; 10:1222–1229.
18. Larsen A, Højlund K, Poulsen MK, et al.: Hypoglycemia-associated electroencephalogram and electrocardiogram changes appear simultaneously. *J Diabetes Sci Technol* 2013;7:93–99.
19. Remvig LS, Elsborg R, Sejling A-S, et al.: Hypoglycemia-related electroencephalogram changes are independent of

### NEUROLOGICAL CHANGES IN HYPOGLYCEMIA

3

- gender, age, duration of diabetes, and awareness status in type 1 diabetes. *J Diabetes Sci Technol* 2012;6:1337–1344.
20. Fruehwald-Schultes B, Born J, Kern W, et al.: Adaptation of cognitive function to hypoglycemia in healthy men. *Diabetes Care* 2000;23:1059–1066.
  21. Hvidberg A, Fanelli CG, Hershey T, et al.: Impact of recent antecedent hypoglycemia on hypoglycemic cognitive dysfunction in nondiabetic humans. *Diabetes* 1996;45:1030–1036.
  22. Dagogo-Jack SE, Craft S, Cryer PE: Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. *J Clin Invest* 1993;91:819.
  23. Howorka K, Heger G, Schabmann A, et al.: Severe hypoglycaemia unawareness is associated with an early decrease in vigilance during hypoglycaemia. *Psychoneuroendocrinology* 1996;21:295–312.

Address correspondence to: ◀AU9  
Maria Rubega ◀AU10

*Department of Information Engineering  
University of Padova  
Padova 35131  
Italy*

*E-mail: maria.rubega@gmail.com*

**AUTHOR QUERY FOR DIA-2017-0009-VER9-RUBEGA\_1P**

AU1: Please review all authors' surnames for accurate indexing citations.

AU2: Please mention the authors' degrees.

AU3: The Publisher requests for readability that no paragraph exceeds 15 typeset lines. Please check for long paragraphs and divide where needed.

AU4: Please check the edit of the sentence "Indeed, during hypoglycemia, the EEG...."

AU5: Disclosure Statement accurate? If not, please amend as needed.

AU6: Please confirm the correctness of Ref. 6.

AU7: Please update Ref. 12 if possible.

AU8: In Ref. 15, please mention the book title, editors' name, publisher's location, and page range.

AU9: Please confirm corresponding author's name and address.

AU10: Please mention the degrees of the corresponding author.