Closed-Loop Systems: Diversity and Natural Selection

When Charles Darwin sailed the HMS Beagle to the Galápagos Islands in 1835, he was moved and inspired by the incredible diversity in the species of finches and tortoises, leading ultimately to the formulation of his ideas on the origin of species and natural selection. One might have been similarly moved during a recent meeting of the Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas Project Consortium, held during the annual Scientific Sessions of the American Diabetes Association—in a somewhat less exotic location in downtown Philadelphia. In the relative absence of selective pressure (i.e., with the generous financial support of the JDRF and the National Institute of Diabetes and Digestive and Kidney Diseases), an incredibly rich and varied bio (engineering) diversity has been allowed to flourish in the environment of closed-loop artificial pancreas research. Multiple species of glucose sensors, insulin pumps, and particularly algorithm and controller designs, combined in various permutations to populate the display tables and research presentations during the meeting. This open environment is appropriate and conducive for the early stages of system development; allowing broad creative and engineering latitude should maximize the likelihood of the generation of successful closed-loop devices. However, now that the first "in-human" feasibility studies are rolling out and researchers, funders, and regulatory agencies are evaluating their early results, the first waves of selective pressures are starting to be felt. Each group has its favorite sensor or pump; the proportional-integrative-derivative (PID) controller proponents defend the relative merits of their algorithms with the model-predictive-control (MPC) crowd, and the investigators provide scientifically rigorous and passionate justifications and rationales for their approaches and devices.

In this issue of *Diabetes Care*, Russell et al. (1) report on the results of their iteration of a closed-loop system, their so-called bihormonal bionic endocrine pancreas, which incorporates one afferent sensor component (Freestyle Navigator; Abbott Diabetes Care, Alameda, CA) and two distinct efferent hormonal outputs, insulin and glucagon, delivered via two separate pumps (OmniPod; Insulet Corp., Bedford, MA), each under individual algorithmic control: an MPC-based controller for insulin and a proportional-derivative–based controller for glucagon. In six adult volunteers with type 1 diabetes, undergoing 48 h of closed-loop control, this system achieved average reference blood glucose levels of 158 ± 44 mg/dL, with 68% of values being within the desired 70–180 target range and only 0.7% of values of <70 mg/dL. The average peak postprandial glucose level was 257 ± 69 mg/dL, achieved with the addition of announced priming boluses of 0.035–0.05 units/kg insulin per meal, administered at the start of the meal.

It appears that the use of glucagon was successful in staving off most episodes of hypoglycemia, particularly in the postprandial period, compared with two previous closed-loop studies using only insulin and a PID controller (2,3). Although overall mean glucose levels were slightly lower (133 ± 52 and 138 ± 50 mg/dL, respectively) and percentage of glucose values within the target range of 70–180 mg/dL was slightly higher (75 and 85%, respectively) in the PID-based system, there was also a tendency to late postprandial hypoglycemia, either before lunch (2) or following dinner (3) when a meal was not provided within 4 h of the prior one. In this current study, minidoses of glucagon, administered in the late postprandial period during periods of falling glucose levels, countered the effect of residual insulin action left over from the previous meal. It is interesting to speculate whether glucagon would still be needed in this setting if the pharmacokinetics and -dynamics of insulin could be improved. It remains to be seen whether strategies to accelerate insulin action, such as infusion site warming (4), coformulation with hyaluronidase (5), or intraportal insulin delivery (6), will resolve this problem of late postmeal insulin "overshoot." Algorithmic approaches to reduce this phenomenon, such as the incorporation of an insulin feedback modification to the PID algorithm, have shown some preliminary efficacy (7), and in our most recent study, use of this PID plus insulin feedback algorithm resulted in the complete avoidance of hypoglycemia during almost 400 person-hours of closed-loop control, along with slightly higher average glucose levels (8).

The use of glucagon in a dual-hormonal system may hold its greatest potential in mitigating the risk of hypoglycemia during and after exercise, a time when subjects with diabetes are at particularly high risk (9). We previously demonstrated that even the complete suspension of basal insulin during exercise is not sufficient to prevent all episodes of hypoglycemia after exercise (10); it is therefore unlikely that a single-hormone closed-loop system can adequately prevent hypoglycemia in the setting of exercise. The extremely low rate of hypoglycemia in the current study, which included a standardized exercise regimen, may therefore justify the added complexity of the system. On the other hand, the unknown long-term effects and potential toxicities of glucagon administration (11), as well as the practical issues related to having multiple pumps and infusion sites, makes one wonder if it would not just be better to pretreat exercise with carbohydrates, as is done in the current open-loop world.

It is tempting but ultimately premature to draw any conclusions about the relative efficacy and safety of the various closed-loop systems, as the populations and clinical protocols are quite different: adults versus children, exercise component versus sedentary only, small versus large meals, and premeal bolus versus no premeal bolus. Furthermore, the engineering laboratory and clinical research unit environments in which these closed-loop species were born in no way resemble the true habitats in which the finished products will eventually live (or die). It is sobering to think that the safety and effectiveness of our current pumps, worth thousands of dollars and methodically tested for precise, accurate, safe delivery of insulin, are ultimately determined by the small pieces of plastic,

fabric, and glue that hold the infusion site in place. So too, will the eventual success or failure of closed-loop systems ultimately be determined not only by how well they function in the sheltered tidal pools of the laboratory or clinical research center but how they can survive in such harsh and hostile environments as the school playground or locker room.

I suspect that, in the end, surviving (and commercially competing) closed-loop systems will each have different strengths and weaknesses; for example, one may handle meals more effectively, while another is better with exercise. As a clinician, then, I will have the opportunity to choose among several effective closed-loop systems, which I can match to the particular needs of my patients, just as I do now for the separate components of their pumps, sensors, and meters. Vive la différence!

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