

Mind over Muscles: Linking Movement to Neurons in Neonatal Diabetes

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The beeps of the machines in the OR are masked by the screeching cry of the newborn. Her parents shed tears of joy as they hold her after nine months of anticipation. They gaze into her blue eyes, thinking little about all the genes within her that make her appear the way she is. From the size of her pudgy toes to the functioning of her brain, her genes control every part of her. The human genome consists of between 50,000 and 100,000 genes, each with their own unique length, location, and function that enable the complex processes to occur within each cell. Replication of these genes occurs at blazingly fast speeds with relatively high accuracy, but when an error occurs, many detrimental effects can result. One such effect is the occurrence of a disease termed iDEND that stands for Intermediate developmental delay, epilepsy, and neonatal diabetes.

Scientists at the University of Oxford explore the origin of the mutation that causes muscle dysfunction in neonates diagnosed with iDEND¹. Previous studies have shown that there is widespread expression of KATP channels, but whether overactive KATP channels in the muscle or the nerve cells are responsible for hypotonia is unclear. Commonly seen in patients with iDEND, hypotonia, is the lack in muscle tone that is believed to be the cause of poor gait in patients¹. To test this, a group of scientists led by Dr. Rebecca Clark in the Department of Physiology, Anatomy, and Genetics at the University of Oxford expressed gain of function mutations in either nerve or muscle cells of mice and evaluated their effects on muscle strength and motor coordination¹.

Three tests were done to evaluate the physiological effects of the mutations in the mice: their ability to hold on to a suspended rotating rod, the time spent on a free-running wheel, and the time spent in spontaneous physical activity. The results from these tests indicate that the mice with mutations in their nerve cells spend significantly less time holding on to the rotating rod and spend substantially more time in spontaneous activity or using the free-running wheel. It was concluded that, as with iDEND patients, nerve-mutated mice are impaired in muscle strength, balance, and motor coordination, indicating that the motor defects initiate at the central nervous system. Interestingly, the scientists noted that the hyperactivity seen in the nerve-mutated mice was similar to behavior seen in children suffering with iDEND. To confirm that iDEND-like physiological effects originated in neuron, scientists recorded the electrical activity of specific neurons called Purkinje cells, known to play an important role in motor coordination. They observed that the action potential frequency was five times less likely to occur in the Purkinje cells of mice with nerve mutations than in control mice. The scientists concluded that the delay in action potential frequency was because the resting potential of these cells was more negative. Additionally, when these cells were exposed to tolbutamide, an inhibitor of KATP channels, there was an increase in action potential frequency while there was no change in the firing frequency in control mice. This observation suggests that the increased KATP current in Purkinje cells suppresses firing and therefore impairs motor function.

For the past 4 years, sulphonylurea therapy has been the preferred choice of treatment in patients with

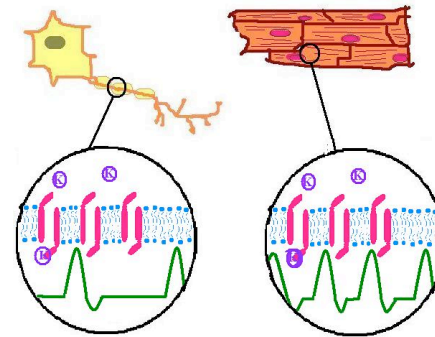


Figure 1: Increased KATP channel current and relatively low frequency of action potentials fired in Purkinje nerve cells (left) compared to muscle cells (right). When exposed to a KATP channel inhibitor, the frequency of action potentials was similar to muscle cells, demonstrating that motor impairment in patients with iDEND originates in nerve cells.

neonatal diabetes or iDEND¹. These drugs lower blood glucose by binding to specific sulphonylurea receptors (SUR), that block KATP channels and cause islet β -cells to secrete insulin². This form of therapy maintains blood glucose levels and improves neurological problems and motor coordination in patients with iDEND². A concern when using this therapy is that when taken in high doses, as those required by patients with neonatal diabetes, these drugs might interfere with the normal functioning of cardiac muscles¹. Since this paper concluded that poor motor coordination in patients with iDEND is neuronal in origin, scientists can work on developing neuron-specific sulphonylurea drugs that are permeable in the blood-brain barrier¹. These drugs would be more effective for correcting motor problem and would have a lower chance of cross-reactivity with cardiac tissue.

Scientists do not know yet if iDEND is the cause of a mutation in one gene or multiple genes, nor are they certain about the type of mutation in humans. The results presented in this paper, however, demonstrate the possibility of improving the lives of those affected by rare genetic diseases. Though new parents are mostly not completely aware, doctors and nurses who deliver babies run a series of observational screening tests that can immediately determine if there may be any abnormal conditions in the newborn. Recognizing signs that indicate that a newborn may have a detrimental condition allows parents to focus on enjoying the miracle of life, while doctors strive to look beyond the physical features into the positive and negative effects of our genes.

References

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²Pearson, E.R., Fletcher, I., et al. (2006). Switching From Insulin to Oral Sulphonylureas in Patients with Diabetes Due to Kir6.2 Mutations. *N Engl J Med.* 355, 467-477

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