Perineuronal Nets: Protection for Memories

By Priya Kudva

French philosopher Descartes once mused, “I think, therefore I am.” Human consciousness is unique among evolved life forms on Earth. We can think, remember, imagine, visualize, deduce, conclude, and expound. These remarkable abilities that humans possess can only be attributed to the brain and its ability to form connections.

Inside the brain are billions of nerve cells called neurons. These cells are much like the cells throughout the rest of the body, but are more special. They are roughly analogous to electrical wiring in a computer. These cells have a cell body (soma) and a tail (axon) that can translate information from the environment into electrical and chemical signals. Using the connections formed between multiple neurons, those signals are translated again into smells, images and feelings that are either new or known. These translations happen through electrical signals called action potentials.

Action potentials are events where the electrical membrane potential quickly rises and falls while traveling along the neuron. This happens when sodium molecules enter the cell to create a brief imbalance of charge (Figure 1) [10], which create the electrical potentials. Because action potentials do not last long, they allow neurons to transport information to other neurons in a fraction of a
second. Neurons are able to do this by releasing a compound called a neurotransmitter. With these action potentials, humans are able to perceive the world as events are happening, which is one reason why we are able to dodge something like a ball moving at 80mph.

But there are more than just neurons in the brain. Around the majority of neurons is a net of fibers and chemicals that protect the neuronal connections and prevent them from disconnecting. However, because humans are always learning new information, the connections in our brains cannot be permanent. And yet, these nets keep the structural plasticity, or ability to form and delete connections to neurons, turned down. These nets of fibers found in both the brain and spinal cord are called perineuronal nets (PNNs).

*What are they?*

PNNs are nets of protein fibers that surround neurons in the central nervous system. They are made of a condensed matrix of proteoglycans, or proteins that have multiple carbohydrates attached, and various link proteins that support these proteoglycans. They act as an insulator for each neuron they surround by keeping the electrical signals from spreading to neighboring cells, much like the insulation for wires. As shown in the figure on the right (Figure 2) [9], there is an image of a specific neuron that has been dyed red wrapped in a perineuronal net that has been dyed green. In 1893, neuroscientist Camillo Golgi drew attention to this fibrous neuronal structure of proteins now known as the perineuronal net. Appropriately, he described them as a “kind of corset of neurokeratin (neural protein fibers) which impeded the spread of current
(electrical flow) from cell to cell.” Perineuronal nets are able to achieve this because of the net-like structure that is able to “trap” molecules close to the cell. Though PNNs act as more of inhibitory structures, they have recently come to symbolize that the neuron they surround is a physiologically mature cell [1].

What is their purpose?

Perineuronal nets have been known to preferentially surround GABAergic interneurons [2], or neurons that regulate gamma-Aminobutyric acid (GABA). GABA is known as the “chief inhibitory neurotransmitter”, because it often plays a key role in reducing excitatory signals. Excitatory means that it will increase the signal with a positive charge, while inhibitory means that it will decrease the signal with a negative charge. PNNs surround this specific type of neuron, because these neurons often output a “high level of neuronal discharge” [2] to create a powerful negative current in the neuron. However, these high levels of discharge can often “leak” if the PNN is damaged or destroyed.

Despite the perfection of the brain, nothing is perfect. There are times when action potentials get “leaked” to neighboring neurons, thereby accidentally exciting an extra neuronal pathway. For example, why do people sneeze after looking at the sun or a bright light? This phenomenon, known as the photic sneeze reflex, could be explained by this action potential “leakage”. The electrical signals that came with the overwhelming amount of light from the sun could overflow through the neuron’s membrane and could affect another neuron; in this instance, the neuron is the one that could initiate the pathway that results in a sneeze. Perineuronal nets are normally able to prevent these action potentials from leaking to other neurons, but not always.
This all happens in a normal brain, but what would happen if the PNNs, the protection from these leaks, were to be damaged or absent? This situation is commonly found in patients that had a stroke, Alzheimer’s disease, or epilepsy. A stroke is characterized by poor blood flow to the brain, which results in cell death and eventually improper brain function. Alzheimer’s disease is characterized by gradual degradation of neurons. Epilepsy is characterized by seizures that are the result of an abnormal amount of electrical activity in the brain. In each of these cases, there were a decreased amount of PNNs in the patients’ brains [3 and 5]. However, there was also evidence that the decrease in PNNs increased the plasticity in their brains [4 and 5]. This means that although there was an abnormal amount of electric activity in the brain, the brain went into a state where change would be easier. This transition of states could signify that the brain is trying to heal itself, a biological phenomenon that humans have been trying to recreate for decades through research.

*What are some perineuronal net research topics?*

Throughout the brain, PNNs have been found to possess similar functions and composition. Even so, PNNs affect each part of the brain differently when tampered with.

In the research on drug addiction, perineuronal nets play a huge role in the deletion and relapse of drug memories. It has been found that if the PNNs have been depleted in the amygdala (the emotions part of the brain), the erasure of drug memories will be enhanced [6]. In other words, it will be easier to ignore and eventually forget about the craving of the drug. However, when the PNNs in the prefrontal cortex are depleted there is a different effect.

The prefrontal cortex is the front-most part of the brain that is often associated with personality and decision-making [7]. When the PNNs are removed in this area of the brain, it has
been found that there is a loss of long-term memory formation, specifically in a fear context [8]. This means that with the PNNs gone, even life-threatening experiences would not be remembered in their proper context, which could cause people to repeat past mistakes and not be so lucky.

As shown, perineuronal nets can have both beneficial and adverse effects on the brain. As researchers continue to discover new aspects of PNNs, and technology advances at an even faster rate, those effects might soon result in being mostly beneficial.

What is the future of research on perineuronal nets?

In the age when the brain is one of the new frontiers in science, every small detail is important. Now that it is known what perineuronal nets can do, it will be easier to see why they are so important to the entire brain. With the continuously advancing technology, it has become easier to manipulate biological components of the brain. But beyond that, it could be possible to create biological components.

One possible research project could be to create artificial PNNs. These PNNs could help the patients with epilepsy or Alzheimer’s disease, who lack these PNNs. Another could be to create a new type of PNN that allows the deletion of the addiction memory, while keeping the fear memory intact. Like Tim O’Reilly said, “What new technology does is create new opportunities to do a job that customers want done.”
References


