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A new role for an old molecule

By Hugo Pedder

Brain tumours are one of the most lethal disorders of the central nervous system that can develop. Whilst they may take several years to kill a patient, death is almost always inevitable. Although the list of genetic markers for tumours continues to expand, our understanding of their mechanisms remains limited, as does our capacity to treat them. Currently, the most effective treatment is brain surgery to remove as much of the tumour as possible. However, this operation itself is rather dangerous, and almost all patients will still eventually die due to the regrowth of the tumour. New treatments are needed to more precisely interrupt tumour development without damaging normal cells. This requires further understanding of the signalling pathways involved in tumour growth so that the cells can be more specifically targeted. I recently found further evidence to suggest that a commonly occurring neurotransmitter in the brain may be involved in tumour growth.

GABA, an inhibitory neurotransmitter

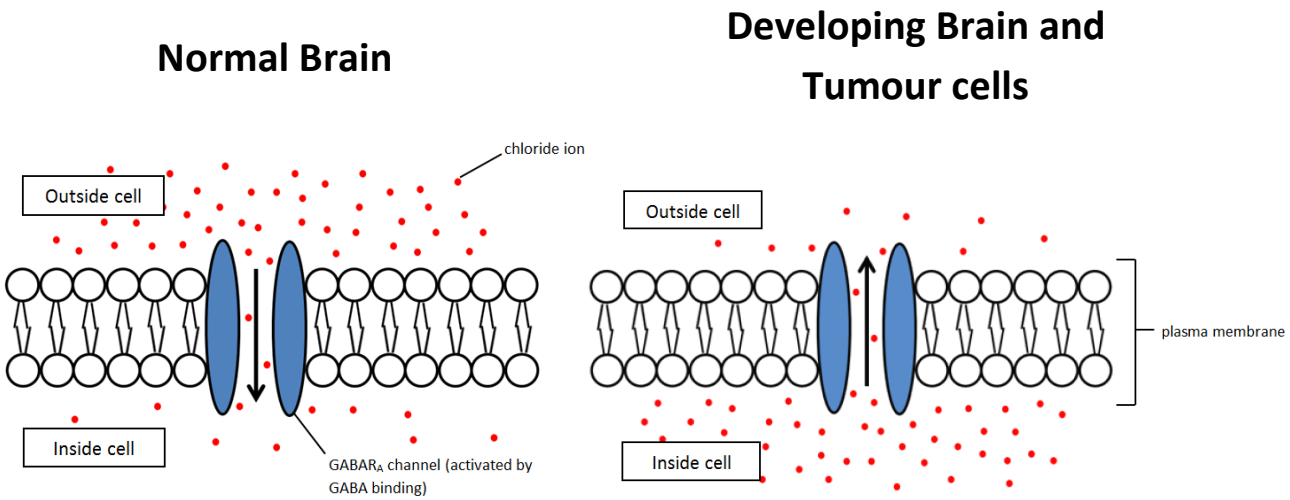
GABA is the most common and most frequently studied inhibitory neurotransmitter in the brain. It plays a role in regulating the excitability of neurones in almost every system in the brain via its binding to GABA receptors. The inhibitory activity of one of the receptor types for this neurotransmitter, $GABAR_A$, is produced by the movement of negatively charged chloride ions into the cell after GABA binding. Each $GABAR_A$ acts as a channel, opening like a gate upon activation. They are each made up of 5 subunits out of the 19 possible subunits that exist, and these different combinations of subunits give each molecule different physiological functions.

GABA in proliferation

Using a newly developed staining antibody, I tested for the presence of four of these subunits in tumour tissue taken from patients after brain surgery, and discovered that different subunits were found to a greater degree in some tumour types than in others. The most striking result was the abnormally high expression of the “theta” and “rho2” subunits in gemistocytic tumours. These are brain tumours which contain a large proportion of gemistocytes, distinctive-looking swollen glial cells whose presence is associated with poorer patient survival. Poorer survival suggests increased tumour growth, which in turn suggests that the theta and rho2 subunits may be involved in tumour cell proliferation. However, $GABAR_A$ subunits are not expressed at all in brain tumours that have even higher rates of proliferation, such as gliobastoma muliforme, indicating that the theta and rho2 subunits’ possible involvement in proliferation is not quite as straightforward as it seems.

Other evidence has also been emerging that $GABAR_A$ may play a role in proliferation aside from its inhibitory activity. The opening of $GABAR_A$ channels in the membrane of neurones allows

chloride ions to pass across the membrane. In the normal brain, since chloride concentrations inside neurones are lower than outside, the opening of the channel inside the membrane of a neurone allows chloride ions to flow into the cell, much like the opening of a dam to allow water to pass through it. However, in the developing brain, chloride concentrations inside cells are *higher* than outside, meaning that when the $GABAR_A$ channel opens, chloride ions flow *out of* the cell. Since this is a reversal of the normal inhibitory action of GABA, it becomes excitatory, an effect which causes immature brain cells to proliferate.



This concentration reversal has also been found in tumour cells, which may mean that in tumours where $GABAR_A$ is found, GABA may affect proliferation to some degree, and that drugs used to block or mimic GABA could be used to prevent brain tumour growth. However, due to the importance of GABA signalling throughout the brain, unselective manipulation of GABA receptors could cause disastrous effects. Since certain $GABAR_A$ receptors composed of specific subunit combinations respond to specific drugs, whilst other combinations do not, developing drugs that target desired $GABAR_A$ receptors with specific subunit combinations may be possible in the future. At present, relatively little is known about the effects of different subunit composition on $GABAR_A$ physiology, so while we want to find out more about GABA in brain tumours, it is just as important to find out more about GABA activity in general, in order to develop the means to manipulate the activity of the receptor.