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Inhibition and over-reaction

Familial startle disease is among the oddest of disorders. The demonstration of a mutation in the inhibitory glycine receptor points towards a cause of this and similar perturbations.

WHEN startled, most people jump, a reflex which is presumably a primitive defence mechanism. It is, perhaps, surprising then that people in whom this reaction is exaggerated (as in patients with startle disease, otherwise known as hyperexplexia) are probably more at risk than those lacking the reflex. In this month's *Nature Genetics*, John Wasmuth and colleagues[1] report that in some hyperexplexia patients a single amino acid is altered in the inhibitory glycine receptor. The many scattered observations surrounding this and similar conditions make more sense in the light of this discovery.

Hereditary hyperexplexia (also called Kok disease) is present from birth, affected infants displaying severe muscle rigidity and an exaggerated startle reflex. The sustained muscle rigidity (hypertonia) gradually subsides over the first year of life, although sufferers often die during this time — hypertonia of the respiratory muscles may mean they stop breathing. Throughout life, the exaggerated startle reflex can be brought on by an unexpected noise or tactile stimulus. The reflex may be accompanied by the severe rigidity which in some cases can cause the patient to become as stiff as a board.

Hyperexplexia is not unique in this respect. Several heritable disorders manifest reflex responses of such seriousness that patients can cause harm to themselves and onlookers. Notable among them is a condition known as Jumping or, more completely, the Jumping Frenchmen of Maine. The condition, first observed in French-Canadian lumberjacks from the Moosehead Lake region of Maine in northern America, has a dramatic phenotype. An exaggerated startle reflex is seen but this is often followed by reflex speech or behaviour. In an address to the American Neurological Association[2] in 1878, George Beard explained these manifestations as follows: "If [an affected individual] was abruptly asked to strike another, he would do so without hesitation, even if it was his mother and he had an axe in his hand". Other reflex reactions include echolalia (repetition of speech), echopraxia (copying a movement or action) and, reminiscent of a characteristic of Tourette's syndrome, coprolalia (speaking obscenities).

Descriptions of Jumping Men are unknown outside the northeastern United States and Canada. But it is difficult to believe that the existence of so-called Goosey individuals, mainly in southern parts of the United States, can be coincidence. In 1980 Hardison[3] described numerous cases of people who had an exaggerated reflex reaction when startled (in particular, when goosed). They demonstrated a marked jump, echolalia, occasional coprolalia and reflex carrying-out-of-commands. Jumping and Goosey may therefore be allelic disorders (or indeed a varying phenotype within the same disorder).

This idea is pure conjecture. But it is lent anecdotal support by an episode, in the second half of the eighteenth century, in which many French Canadians were expelled from the Maine area because they refused to swear allegiance to the British Crown. They fled to the southern states where many of them settled, and where Goosey seems to be most prevalent.

That behavioural disorders such as these can be a consequence of genetic mutation is intriguing. Moreover, Wasmuth and colleagues' report comes as something of a breath of fresh air. In each of six (soon to be seven) recent cases in which the genetic defect associated with a neurological condition has been characterized, that defect has been expansion of an unstable triplet repeat sequence[4]. With a single amino-acid substitution in a subunit of the glycine receptor, hyperexplexia is clearly an exception; and the new work has other unusual characteristics.

Hyperexplexia patients can be successfully treated with clonazepam, a benzodiazepine known to enhance γ-aminobutyric acid (GABA) neurotransmission. The sequence and structure of the GABA receptor is very similar to those of the glycine and glutamate receptors. Using a standard linkage approach, Wasmuth and co-workers had previously uncovered linkage of hyperexplexia to the long arm of chromosome 5 and found the area to be uncommonly rich with good candidate genes, including those coding for two subunits of the GABA receptor (GABRA1 and GABRA2), a glutamate receptor (GLUR1) and a subunit of the glycine receptor (GLRA1). Spoilt for choice, the authors used radiation hybrid analysis to further localize these genes and were able to show that GABRA1 and GABRA2 fell outside the hyperexplexia candidate region whereas GLRA1 was within it. They also found that the glycine receptor is antagonized by strychnine which, when administered to mice, causes hypertonia and an exaggerated startle reflex. So a good candidate gene became an excellent one and they started screening GLRA1 in affected patients and their families. Four of the seven families studied showed evidence for mutations, all of which involved the substitution of the same amino acid in the mature protein.

In an accompanying News and Views article[5], Floeter and Hallett point out that the commonly held view within the neurological community, that hyperexplexic patients show a hyperexcitability within the reticular formation of the brain stem, does not tie in with the new findings, because the glycine receptor is found only at relatively low levels in the reticular formation. But they go on to explain that although the acoustic startle response in hyperexplexic patients is essentially normal, with patients just being more sensitive to sound and demonstrating a greater response to it, they do respond abnormally to other stimuli. Taps on the nose and experimental electrical stimulation of the peripheral nerves also lead to a tremendous response. But such responses clearly involve the central and peripheral nervous systems, which implies that hyperexplexia may be a generalized neural hyperexcitability of normal pathways (rather than being restricted to a certain area of the central nervous system), and that the startle response may simply be the most prominent manifestation of this generalized hyperexcitability.

This idea fits in much better with the findings of Wasmuth and colleagues. Glycine is known to inhibit signals of the nervous system by binding to chloride ion-channel receptor complexes, a process which takes place in at least two populations of glycinergic inhibitory interneurons connected to motor neurons of the central nervous system. Hence a defect in the glycine receptor would result in a removal of an inhibitory loop, and could therefore explain some of the characteristics of hyperexplexia and possibly other inherited startle disorders.

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