LETTER TO THE EDITOR

Parkinson's disease, DBS and suicide: a role for serotonin?

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Sir, High frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) using surgically implanted electrodes is an effective treatment of advanced and otherwise treatment-resistant Parkinson’s disease (Kumar et al., 1999; Krack et al., 2003; Rodriguez-Oroz et al., 2005; Visser-Vandewalle et al., 2005; Deuschl et al., 2006). Despite having important beneficial motor effects, STN DBS can be associated with unpleasant and debilitating psychiatric effects (Bejjani et al., 1999; Piasecki and Jefferson, 2004; Temel et al., 2005, 2006), which may mitigate the positive effects on motor symptoms. The psychiatric problems linked to STN DBS are highlighted in a recent report in Brain by Voon et al. (2008). In this report, retrospective analysis of over 5000 Parkinson’s disease patients treated with STN DBS in research centres across the world, revealed a striking increase (~15-fold) in suicide rate in the first year post surgery, which declined but was still greater than controls at 4 years follow up. Suicide attempts and completed suicides were significantly associated with post-operative depression and a previous history of impulse control disorder.

The report by Voon et al. provides the first systematic measure of risk of death through suicide but over the last decade many single centre studies have noted the disabling mood and cognitive side effects of STN DBS, as well as its propensity to induce suicidal ideation and actions (Rodriguez et al., 1998; Kumar et al., 1999; Moro et al., 1999; Houeto et al., 2000; Molinuevo et al., 2000; Dujardin et al., 2001; Volkman et al., 2001; Berney et al., 2002; Doshi et al., 2002; Houeto et al., 2002; Martinez-Martin et al., 2002; Ostergaard et al., 2002; Romito et al., 2002; Thobois et al., 2002; Valdeoriola et al., 2002; Vingerhoets et al., 2002; Krack et al., 2003). The mechanism by which DBS STN causes mood-related changes is unknown but DBS modulation of connections between the STN with forebrain areas such as the prefrontal cortex areas have been proposed (Hershey et al., 2004; Temel et al., 2005, 2006). However, there are long-standing links between suicide, depression, impulsivity and mid-brain serotonin neurones (Mann, 2003; Cowen et al., 2006), which are the source of an extensive serotonin innervation to the limbic forebrain (Booij et al., 2006; Wrase et al., 2006).

In a recent preclinical study, we reported that high frequency stimulation of the STN inhibited the electrical activity of serotonin neurons in the dorsal raphe nucleus of the mid-brain (Temel et al., 2007). This effect was both region- and neurone-specific, and was only apparent at clinically relevant stimulation parameters. Interestingly, we found that STN stimulation also evoked depressive-like behaviour in a rodent model of Parkinson’s disease, which was reversed by a serotonin selective antidepressant, thereby linking the behavioural change to the decrease in serotonin neuron activity. Although direct connections between the STN and mid-brain raphe are sparse, several brain regions that provide important inputs to the dorsal raphe nucleus (including the substantia nigra pars reticulata and lateral habenula nucleus) are also targets of STN outputs (Smith et al., 1997). These convergent pathways are potential substrates for the inhibitory effect of STN stimulation on the firing of serotonin neurones and the associated behavioural changes.

We speculate that the decrease in serotonin transmission elicited by STN stimulation in our preclinical experiments is causally linked to the risk of post-operative depression and subsequent suicidal behaviour after DBS STN observed in recent clinical studies, and...
systematically documented by Voon et al. This idea certainly fits with findings that in patients at risk of depression, depletion of the serotonin precursor tryptophan increases depressive symptoms and induces impulsivity (Booij et al., 2006), as well as findings that tryptophan depletion produces similar effects in Parkinson’s disease patients (McCance-Katz et al., 1992). If, as we propose, depressive symptoms and suicidal behaviour induced by DBS STN involves a serotonin-dependent mechanism, then there is a clear rationale for using serotonin-targeted manipulations both to manage these side effects and even detect patients at risk.

References


