LETTER TO THE EDITOR

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

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We would like to thank Temel et al. for their communication highlighting the potential role of serotonin and suicidal behaviours, which are intriguing and potentially of relevance. Temel et al. have previously shown that subthalamic nucleus (STN) HFS in a rat study inhibits serotonergic dorsal raphe firing rate and elicits depressive-like behaviour which can be prevented with pre-treatment with a serotonin reuptake inhibitor (Temel et al., 2007). Post-mortem and biological challenge studies suggest serotonergic hyporesponse particularly in suicide attempts of high lethality and lower prefrontal serotonin receptor density with a compensatory increase in midbrain serotonin neuron density and function (Mann et al., 1996; Oquendo et al., 2003; Boldrini et al., 2008).

Temel et al. point to a potential mechanistic link between serotonin and post-surgical suicidal behaviours mediated via depression and impulsivity, which is less clear and very complex. In our paper, we identified an association between suicide attempts and post-STN HFS depression (Voon et al., 2008). However, the link between STN HFS and depression is poorly understood in human studies and there are likely several different mechanisms leading to a similar depressive phenomenology. Postsurgical depression can be conceptualized as being mechanistically related to STN HFS itself, dopaminergic medication changes, psychosocial factors, Parkinson’s disease-related depression or premorbid vulnerability to depression (Voon et al., 2006). Temel et al. implicate STN HFS-related depression secondary to serotonergic inhibition, which may be one possible mechanism. The majority of STN HFS studies report an improvement of post-surgical depressive symptoms as measured using rating scales. Systematic assessments of STN HFS have been associated with acute mood changes (Okun et al., 2003) and case studies have reported depressive mood states (Tommasi et al., 2008), but not with long-term depressive symptoms. In contrast, there is also clear association with STN HFS and hypomania (Mallet et al., 2007). Post-STN HFS depression based on case ascertainment has been reported in single centre uncontrolled studies as the authors indicate; however, well-designed randomized controlled trial studies comparing STN HFS and medical treatment or...
unilateral STN HFS and unilateral HFS targeting the globus pallidus interna did not demonstrate any differences in mood changes (Witt et al., 2008; Okun et al., 2009). Similarly, STN HFS for obsessive compulsive disorder did not affect depressive symptoms; rather, the predominant side-effect appeared to be hypomania rather than depression (Mallet et al., 2008). This suggests that factors other than STN HFS itself may be associated with post-surgical depression. Depressive and apathy symptoms have been well-established to arise from dopaminergic medication withdrawal which responds to an increase in dopaminergic medications (Funkiewiez et al., 2006; Czernecki et al., 2008). Furthermore, if postoperative depression is related to Parkinson’s disease depression, this appears to be more likely to be related to pre-synaptic noradrenergic and dopaminergic activity (Remy et al., 2005) with better response to tricyclic antidepressants rather than SSRIs demonstrated in a well-designed randomized controlled trial study (Menza et al., 2009). An individual premorbid risk towards depression may also heighten the risk for postoperative depression, which may be related to various neurotransmitters. Multiple psychological changes including motivation for surgery, and changes in identity and relationships may also impact on mood and respond preferentially to psychotherapy.

The relationship between serotonin, impulsivity and suicidal behaviours is also not clear-cut. Whereas serotoninergic function is associated with high lethality suicide attempts, lower lethality suicide attempts are associated with greater impulsivity as measured using questionnaires and greater prefrontal activity (Oquendo et al., 2003). Suicidal behaviour has been associated with impairments on the Stroop task which measures both response conflict and response selection although this impairment may occur in the context of general cognitive dysfunction (Keilp et al., 2001). Intriguingly, STN HFS is also well-established to be associated with Stroop impairments (Witt et al., 2008). However, in the general population lowering central serotonin levels using tryptophan depletion improves performance on the Stroop task (Evers et al., 2006). Thus, although a potential link may exist between response conflict cognitive correlates of suicidal behaviour and STN HFS, this does not appear to be mediated by lower serotonin levels.

Impulsivity can be parsed into impulsive action, motoric impulsivity, impulsive choice and rapid decision-making. STN lesions in animal studies and STN HFS in human studies have varying effects on different measures of impulsivity. These measures have not been adequately studied in suicidal behaviours. The relationship between serotonin and impulsivity is similarly complex. For instance, serotonergic effects on impulsive action may differ dependent on global serotonin levels and receptor subtype (Winstanley et al., 2004a, b). The serotonergic effects on motoric impulsivity may differ dependent on type of motor response inhibition measured (Eagle et al., 2009). And animal and human studies have reported both an increase and a lack of an effect of modulation of serotonin on impulsive choice (Winstanley et al., 2004a; Schweighofer et al., 2008).

Thus, the presence of impulsivity or depression post-STN HFS may not necessarily be related to low serotonin levels and does not present an easy rationale for SSRIs. SSRIs have not been associated with greater suicide risk in adult populations (Simon et al., 2006; Gibbons et al., 2007). However, individual reactions can vary and SSRIs can be associated with anxiogenesis on an individual level and may thus exacerbate suicidal ideation. Notably, there is intriguing evidence for a link between dopamine, depression and impulsivity; however, we did not address this issue in this response to the letter. We had further identified a decrease in dopaminergic medication as a potential factor associated with postoperative suicide attempts (Voon et al., 2008).

Notwithstanding the complexity, the need to identify subjects at high risk for post-surgical suicidal behaviours is needed. A general algorithm is presented for the assessment of suicidal ideation or suicidal behaviours. Preoperative assessment should include a psychosocial assessment highlighting potential risk factors for suicide attempts. Patients at higher risk should be counselled preoperatively along with family involvement and followed more closely postoperatively. Preoperative antidepressants, mood stabilizers, antipsychotics and benzodiazepines should be maintained to prevent withdrawal states. For patients at higher risk, dopaminergic medications should be titrated carefully: those with a premorbid history of medication-induced impulse control behaviours should have faster titration and those with a propensity for depression should have a slower titration. If an attempt occurs, issues of safety should be considered including the need for certification, hospitalization and observation with a sitter or with family and education of the patient and family. A psychiatric assessment should be instituted. If depressive or apathy symptoms are present, the aetiology and whether the symptoms require treatment should be considered. If this is likely to be related to withdrawal state, then dopaminergic medications should be considered. If this is likely related to Parkinson’s disease-related depression, then either resumption of a dopamine agonist or an antidepressant with noradrenergic properties may be considered. Based on anecdotal evidence, postoperative depression can also respond to SSRIs. Identification of a time-limited confusional state may require careful observation and if absolutely necessary, a low dose of an atypical antipsychotic. Identification of hypomania should be managed with either a change in stimulation parameters or a decrease in dopaminergic medication dose. Finally, the psychosocial situation should be addressed including changes in family relationships, work and identity, and either psychosocial counselling or family therapy be instituted.

References

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