Suicide and Serotonin: Making Sense of Evidence

Sir,

Suicide is a complex psychosocial behaviour. The stress diathesis model proposed for suicide provides a background to understand how suicide behaviour can be linked to underlying neurobiological abnormalities. Most consistent neurobiological abnormality implicated in the genesis of suicidal behaviour is that of serotonin. Abnormalities in number of serotonergic neurons, serotonin transportation, receptor binding and serotonin levels in key brain areas have all been linked with suicide.[1]

However, there remains some disagreement on the direction of individual findings. For instance, it is well-documented that the cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, are decreased in individuals who attempt suicide. At the same time, increased numbers of central serotonergic neurons and increase in concentrations of tryptophan hydroxylase (key enzyme involved in the synthesis of serotonin) and serotonin levels have also been reported.[1] The latter should logically suggest an increased turnover of serotonin in the brain, whereas the former suggests otherwise. Interestingly, functional imaging studies have demonstrated decreased serotonin transporter binding in attempted suicide[2] while studies using quantitative receptor autoradiography have noted higher $5HT_{1A}$ receptor binding in brain stem and prefrontal cortex.[3]

It is challenging to try and reconcile these findings in order to provide a meaningful model for the role of serotonin in suicide. One way of making sense of the divergent findings is by using the explanation of homeostasis. Given that there is a decreased turnover of serotonin in the brain leading to decreased 5-HIAA levels, it appears plausible that most of the other changes that point the other way, including more serotonergic neurons and reduced transporter binding, could be compensatory in nature. But, why is there low serotonin to begin with? The answer, perhaps, may lie in the up regulation of serotonin $5HT_{1A}$ receptors reported in various studies of suicide.[4] As it is essentially an auto receptor, increased numbers would mean lower net serotonin release and lower serotonin activity, thus forcing the body to invoke compensatory mechanisms to increase serotonergic activity at nerve terminals. The reasons for up regulation of the $5HT_{1A}$ receptor are mostly speculative at this stage and include possible genetic or epigenetic effects of childhood adversity.[5] This may lead to homeostatic up regulation of mechanisms aimed at increasing serotonin bioavailability.

To conclude, various lines of evidence point to the central role of serotonin in suicide. However, there is no consistency between these findings, making it difficult to interpret. It appears that genetic and epigenetic factors may hold the key in understanding the molecular mechanisms underpinning individual vulnerability to suicide. The $5HT_{1A}$ receptor may be crucial to the whole suicide process and also play a role in the neural circuitry affecting mood regulation and decision-making. Future research needs to address the possible link between the homeostasis model and the biopsychosocial model for suicide. Further research is also required on the role of other neurotransmitters implicated in suicide such as glutamate and their interaction with serotonin system given that abnormalities in serotonin alone are unlikely to satisfactorily explain the complex phenomenon of suicide.

Vikas Menon, Shivanand Kattimani

Department of Psychiatry,
Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry, India

Address for correspondence: Dr. Vikas Menon, Department of Psychiatry, Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry - 605 006, India.
E-mail: drvmenon@gmail.com

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