Is there a biology of suicide?

Kevin M Malone

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The importance of a psychiatric disorder in suicidal acts, including suicide, is underscored by the much-replicated finding that about 90% of completed suicides have a diagnosable Axis I psychiatric disorder at the time of death.[1]

From recent studies in Ireland[2] and other countries, alcohol abuse/dependence is the most common psychiatric disorder, followed by depression. However, far more people have psychiatric disorders who will never carry out a suicidal act including suicide. This has led researchers to examine factors within the individual that predispose them to suicidal acts during times of stress, such as an Axis I psychiatric episode.

A stress-diathesis (trigger/threshold) model for suicidal acts including suicide has been proposed, whereby a suicidal act is the result of a combination of a stress (trigger) in a predisposed/vulnerable individual (threshold).[3,4]

The first clue that there may be a biological component to the threshold for suicidal acts arose 25 years ago, when the brains and spinal fluid of a small group of psychiatric patients who had completed suicide were studied. They were found to have lower spinal fluid metabolite of the brain neurotransmitter serotonin, regardless of psychiatric diagnosis.[5] At the time, serotonin was known to be one of the monoamines associated with depression, and low serotonin in suicide was linked with the prevailing monoamine theories of depression. Shortly after this report, further brain studies reported that serotonin-2 receptors in the frontal cortex of the brain were increased in suicide victims.[6]

In anatomical terms, it was known that serotonin was synthesised in the brain stem (the raphe nucleus) and serotonin neurons projected from the brain stem throughout the brain cortex, particularly the medial frontal cortex. As the body routinely compensates for reduced neurotransmitter concentration or availability (or 'signal') by increasing receptor density, increased serotonin receptor populations in suicide victims suggested a biological compensatory mechanism for reduced serotonin.

Since those early reports, 12 of 17 studies on brains of suicide victims have supported these findings. The most recent study identified that not only was serotonin reduced in the brain stem of suicide victims, but that significant alterations were noted within specific regions of the medial prefrontal cortex of the brain.[7,8] In live patients, reduced serotonin levels have been associated with more lethal suicide attempts,[9,10] and there is early evidence that serotonin activation may soon be assessable in live patients using brain positron emission tomography.[11]

The frontal cortex of the brain is the most 'recent' evolutionary organ in man, and is known to be closely associated with mood regulation, decision-making and executive reasoning *('will I/won't I, should I/shouldn't I?')*. The knowledge that the frontal cortex is rich in serotonin projections from the brain stem led biological suicide researchers to hypothesise that serotonin may be intimately involved with these critical psychological functions.

Data from animal studies also suggested that fluctuations and artificial manipulations of brain serotonin levels and availability of serotonin resulted in alterations in animal mood and behaviour.[12] It was thus hypothesised that serotonin may be a key neurotransmitter in the regulation of restraint and in the suppression of unwanted impulses associated with executive reasoning.

During a stressful period such as a major psychiatric episode, it is clinically apparent that ideas of hopelessness and that 'life is not worth living' are common. Suicidal ideas occur in most psychiatric conditions. In general, these suicidal ideas are unwanted and the individual activates pathways within brain executive reasoning centres to suppress the unwanted ideas and images of death by suicide. Successful suppression of these unwanted ideas may depend in part on a threshold of brain serotonin neurotransmitter function, in addition to interpersonal and environmental cues promoting life over death by suicide.

Brain serotonin system function is dependent on a variety of factors. Males have significantly lower serotonin function than females. Serotonin function declines with age. It may be influenced by diet (cholesterol, fatty acids and tryptophan[13]) and alcohol. Alcohol in particular appears to affect serotonin neurons in the brain stem of suicide victims, as well as reducing serotonin transporter function within the prefrontal cortex.[7,8]

Given the close association between alcoholism and suicide, apart from the environmental consequences of alcohol abuse and the risk of depression, destruction of inhibitory brain pathways can only increase the risk of suicide secondary to alcohol. The increase in Irish suicide rates, particularly amongst younger males, may in part be explained by the rise in youth alcohol consumption in Ireland and its suggested toxic effects on sensitive brain neurotransmitter pathways, which protect against suicidal impulses in the context of depressive feelings and dysphoria.

Serotonin level regulation is, evidently, at least partially under genetic influence. Genetic variations in the coding for tryptophan hydroxylase (the rate-limiting step in serotonin synthesis) have reportedly been associated with increased expression of suicidal acts.[14] Brain serotonin levels are also altered by body hormones, particularly the stress hormone cortisol and also by oestrogen across the menstrual cycle in healthy women,[15] and in premenstrual depression.[16]

Ireland has much to offer the international field of suicide research. Well-conducted cross-sectional and longi-

Kevin M Malone, MD, MRCPsych, Consultant Psychiatrist/Senior Lecturer, Department of Adult Psychiatry, Mater Hospital, Eccles St, Dublin 7, Ireland.

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tudinal clinical and biological studies in representative community populations, which are technically possible in Ireland, are extremely difficult (logistically and financially) to do in Europe and the USA.

Moreover, these studies can lay the platform for intervention, treatment and prevention studies that can be scientifically evaluated, and serve as models for other communities who logistically cannot conduct them. As suicide research intensifies in Ireland in response to the alarming increase in suicide rates particularly, but not exclusively, in younger males, it is important not to neglect research findings from the 'biology of suicide' scientists and to include well-designed biological studies in our Irish suicide research repertoire.

Understanding of the biology of suicide is in its relative infancy, and further discoveries may have important consequences for the pharmacological treatment of suicidal depression.[17] Perhaps Irish suicide research can make a contribution to this scientific domain.

Kevin M Malone is Principal Investigator of the Ireland North/South, Urban/Rural Epidemiologic (INSURE) Collaborative Project on Suicidal Behaviour in Major Psychiatric Disorders.

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