Another marker for different types of depression

Lerer and Macciardi (2002) mention predictors of response to various mood-stabilizing agents, including demographic and clinical characteristics, personality features, biological markers and psychophysiological features. These workers conclude that the above predictors of response are not robust enough to be clinically relevant and thus have not been helpful in the emerging field of pharmacogenetics. One predictor not mentioned by these authors is the variable response to the exogenous opioid, psychotropic analgesic nitrous oxide (PAN) in depressive patients (Gillman, 1984; Gillman and Lichtigfeld, 1994; Lichtigfeld and Gillman, 1985, 2002).

The first indication of this differential response to nitrous oxide was described by Zádor (1928) using anaesthetic concentrations of nitrous oxide. He observed that endogenous depressions were often resistant to the effects of the gas, whereas reactive depressions responded positively. These findings stimulated our work.

A pilot study of 24 cases of depression was undertaken in which the effects of non-anaesthetic concentrations of nitrous oxide were investigated, such that the patient was fully conscious, coherent and cooperative throughout the administration (Gillman, 1984). Nitrous oxide was titrated until the symptoms of the depression were lifted or not affected. In recalcitrant cases, a maximum of 9 l of nitrous oxide mixed with oxygen was given. In all cases, the nitrous oxide was given for approx. 20 min, but never longer than 30 min. At all times a minimum of 30% oxygen was administered with the nitrous oxide. Of the 24 patients studied, 20 responded positively and 4 were recalcitrant. After the trial it was found that the responders had been diagnosed as reactive and/or neurotic depression, whereas the non-responders had been diagnosed as endogenous depression. Since this work was completed in the early 1980s and psychiatric nosology was not as exact as it is today, it is possible that some of the responders may well have been suffering from endo-reactive depression (or unipolar depressive disorder).

At the time, it was suggested that there was underactivity of the endogenous opioid system in depression (Gillman, 1984), which could explain the positive therapeutic actions of PAN (Gillman and Lichtigfeld, 1994; Lichtigfeld and Gillman, 1985).

More recently the hypothesis in which depression can arise from underactivity of the opioid system has been supported by other investigations. For instance post-mortem examination has revealed increases in μ-opioid receptor density, but not in affinity, in the brains of suicide victims (Gross-Isseroff et al., 1990). And the prolactin response to exogenous opioids in depression strongly suggests opioid sub-sensitivity. However, this decrease of prolactin response in depression also occurs in response to TRH and also to drugs enhancing serotonergic neurotransmission. As a result, these authors suggest that other mechanisms, apart from sub-sensitivity of opioid receptors, may also be involved in the pathogenesis of depression (Zis and Garland, 1991); a point made in earlier work (Gillman, 1984). Since there is strong evidence for tonic inhibitory opioidergic mechanisms in the human hypothalamic-adrenergic axis, an increase in ACTH and cortisol plasma levels in some of these patients (Zis and Garland, 1991), supports this mechanism. Cortisol secretion escape from morphine suppression could also be wholly or partially the result of opioid receptor sub-sensitivity. However, this response only occurs in a small number of depressed patients (Zis and Garland, 1991). It is therefore possible that patients who demonstrate early cortisol secretion escape from morphine suppression might fail to respond positively to PAN (Gillman and Lichtigfeld, 1994; Lichtigfeld and Gillman, 1985). Where morphine is still able to suppress cortisol secretion in some depressed patients, it would suggest the possibility that the endogenous opioid system is still relatively intact, in which case an exogenous opioid, such as PAN, would probably activate the endogenous opioid system, thereby lifting the depression. This hypothesis tallies with the findings reported above (Gillman, 1984). Seventy-five per cent of the beneficial action of antidepressants have been ascribed to a placebo response (Kirsch and Sapirstein, 1998; Lichtigfeld and...
Gillman, 2002), which may be mediated by the endogenous opioid system (Lichtigfeld and Gillman, 1992). Thus it is not, perhaps, surprising that the endogenous opioid system may be directly involved in the pathogenesis of depression. This possibility is strengthened by the successful use of buprenorphine (Bodkin et al., 1995) in the treatment of refractory unipolar non-psychotic major depressive disorders. It is possible that our one-off use of PAN as a test to differentiate between reactive and endogenous depressions could be duplicated by other opioids, including buprenorphine.

References


Frederick J. Lichtigfeld and Mark A. Gillman
South African Brain Research Institute, 6 Campbell St, Johannesburg, South Africa