Psychopharmacology (1986) 90:422

Psychopharmacology

Letter to the editors

Why do some antidepressants promote suicide?

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It is well known that antidepressant drugs, which preferentially enhance the drive and counteract psychomotor retardation in depressed patients, may promote suicidal tendencies (Benkert and Hippius 1980). Most of these drugs are relatively selective inhibitors of noradrenaline (NA) re-uptake. This neurotransmitter has been supposed to regulate the impetus or drive, whereas serotonin (5-HT), the other monoamine of the "serotonin-noradrenaline link hypothesis of affective disorders" (Sulser 1983), seems to be more involved in mood regulation. Low levels of the major 5-HT metabolite, 5-hydroxyindole acetic acid, in cerebrospinal fluid have been suggested to represent biochemical suicide predictors (Asberg et al. 1976).

We are currently studying the modulation of NA and 5-HT release in the hippocampal formation and some of our *in vitro* results may explain why certain antidepressants, especially those which selectively block NA re-uptake, may promote suicidal tendencies. We suggest that these drugs by enhancing noradrenergic transmission, at least initially reduce the activity of 5-HT neurons: hence in a situation of even more depressed mood (decreased postsynaptic 5-HT levels) similar drugs may provide the patient with enough drive (increased postsynaptic NA levels) to commit his fatal act.

Our suggestions are based on the following experimental observations: first, the electrically evoked 5-HT release in the rabbit hippocampal formation (our experimental model) is inhibited by endogenous NA released from neighbouring noradrenergic nerve terminals via presynaptic α_2-adrenoceptors: the antidepressant (+)oxaprotilin, which increases the biophase concentration of NA by selectively blocking its re-uptake, significantly reduced 5-HT release (Feuerstein et al. 1985). This observation also explains the apparent supersensitivity of these α_2-adrenoceptors following noradrenergic denervation (Benkirane et al. 1985): endogenous NA no longer competes with exogenous agonists for these receptors (Ellison and Campbell 1986). Secondly, NA release in the rabbit hippocampal formation seems not to be reduced but even enhanced by endogenous 5-HT (Feuerstein and Hertting 1986): 6-nitroquipazine, which selectively inhibits 5-HT re-uptake, significantly increased NA release; in addition, various 5-HT receptor agonists, including 5-HT itself, similarly facilitated NA release.

If these findings in the rabbit hippocampus represent general phenomena applying also to humans, the following psychopathological conclusions of possible therapeutic importance may be drawn:

1. The suicide promoting side effect of selective inhibitors of NA re-uptake may be due to the indirect impairment of serotoninergic function as a consequence of increased NA levels. It is well known clinically that the regained drive of similarly treated depressed patients is accompanied by impaired rather than by elevated mood. The disappearance of their sadness seems to be hindered, whereas the relief from their pathognomonic psychomotor retardation may promote suicidal actions which were impossible to perform before, despite the presence of suicidal thoughts.

2. Antidepressants of the "first generation" which unselectively block the uptake of both NA and 5-HT seem to be preferable in patients with psychomotor retardation and high suicidal risk, since the partial 5-HT uptake inhibition may counteract the decrease of 5-HT release following increased endogenous NA.

3. Selective inhibitors of 5-HT re-uptake may enhance the drive of the patients indirectly by increasing NA release via increased levels of endogenous 5-HT. Like unselective re-uptake inhibitors, these drugs should be preferable in patients with high suicidal risk.

4. The "biomolecular linkage between serotoninergic and noradrenergic neuronal systems in brain at the level of the (postsynaptic) noradrenaline receptor coupled adenylate cyclase" (Sulser 1983) should be considered also from a presynaptic point of view.

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Received May 26, 1986; accepted June 2, 1986