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Cholinergic–Monoamine Systems, Depression, and Panic

To the Editor:

Janowsky et al. (1972) suggested that aberrant cholinergic mechanisms may be involved in the pathogenesis of depression, but the possibility that cholinergic systems may be linked to the pathophysiology of panic disorder, an entity related to depressive disorders, has not yet been proposed. There is some reason to hypothesize that this link exists. I would like to suggest that it may be of heuristic value to consider a possible role for abnormal interaction of cholinergic and aminergic systems in the pathogenesis of coexisting major depressive disorder (MDD) and panic attacks.

Leckman et al. (1983) demonstrated the association of panic and depressive disorders. MDD combined with panic disorder in index probands predicted a marked increase in the incidence of both disorders in first-degree relatives. The authors suggested these disorders may share underlying mechanisms. Janowsky et al. (1983, 1984, 1985) have laid a foundation for discussing this topic. These investigators proposed that effects of stress and anxiety may be mediated by muscarinic cholinergic systems possessing a capacity to activate adrenergic networks. Acetylcholine can simultaneously produce behavioral, cardiovascular, and neuroendocrine effects characterizing stress, anxiety, and MDD. There is evidence that cholinergic systems are involved in the pathophysiology of the affective disorders. Cholinergic overdrive produces depressed affect and somatic and psychic symptoms of spontanously occurring anxiety (Rowntree et al. 1950; Bowers et al. 1964; Dilsaver et al. 1983). Central cholinergic systems also regulate blood pressure and heart rate and activate adrenergic neurons associated with elevation of these parameters (features of anxiety and stress response) (Brezenoff 1973; Brezenoff et al. 1979; Brezenoff and Gioliano 1982). The hypothesis that abnormalities of the interregulation of cholinergic and monoaminergic systems account for the association of panic and affective disorders could be a testable means of bridging the pathophysiologies of these disorders. Epidemiological studies and pharmacological investigations lend themselves to this hypothesis.

Nearly 50 years ago, Lindemann and Finesinger (1940) reported that norepinephrine and methacholine, a peripherally active muscarinic agonist, produced panic attacks in 11/20 and 9/20 patients with histories of panic attacks, respectively. Thus,

cholinergic and aminergic drugs can produce a panic attack in susceptible subjects. Granted, this may be a nonspecific effect. Specificity would be an issue that needs to be examined. However, the effectiveness of these drugs in producing the attacks is consistent with autonomic physiology. Muscarinic agonists precipitate release of catecholamines from the adrenal medulla and cardiac tissues. This effect is so potent that an organism that is initially in a hypercholinergic state can quickly enter a hyperadrenergic state. Small doses of intravenously administered acetylcholine produce bradycardia, generalized vasodilatation, and a fall in blood pressure. However, these initial effects are quickly followed by reflex tachycardia and vasoconstriction via a baroreceptor response. In sufficient doses, acetylcholine stimulates the release of catecholamines and activates sympathetic ganglia (Taylor 1980). These latter effects bring about the hypercatecholaminergic state.

Pathologically perturbable cholinergic systems threaten to mobilize monoaminergic networks (Dilsaver and Greden 1984). There is strong evidence that this occurs. In addition to findings noted above, several other points are also supportive. Muscarinic agonists cause (1) "vagal" effects—which are alone characteristics of fright or severe fear, and (2) release catecholamines (epinephrine and norepinephrine) from the adrenal medulla. Epinephrine leads to a β-adrenergic effect and a greater reduction in blood pressure due to vasodilatation. Muscarinic agonists also act directly upon central mechanisms regulating neurovegetative functions and α-adrenergic neurons to trigger the release of norepinephine. For example, there are muscarinic receptors on adrenergic neurons (Ehlert et al. 1983; Sorscher and Dilsaver 1985) which promote the release of norepinephrine.

Elegant means of testing the hypothesis proposed are not currently available, but basic strategies are possible. For example, the locus ceruleus has been implicated in the genesis of anxiety states. This structure interacts with cholinergic structures in the regulation of REM–non-REM transitions and can be functionally isolated in order to study the physiology of sleep in intact animals. These studies, recently reviewed by Dilsaver and Greden (1983), provide a model after which the interaction of cholinergic and monoaminergic systems in the pathophysiology of coexisting MDD and panic might be patterned.

In conclusion, the hypothesis set forth is of potential value in studying the pathophysiology of panic disorder occurring in the context of affective disease. Panic disorder outside of this context may be a different etiological entity.

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Within-session Data

To the Editor:

Early studies on neuroleptic effects in animal behavior paradigms revealed response suppression in several different tests of unconditioned motor behavior (Dews and Morse 1961). Although recent hypotheses suggest that decreases in spontaneous activity may be more related to motor side effects (extrapyramidal symptoms) in the clinical situation than to antipsychotic properties, overall rate reductions in these procedures continue to be used for characterizing the behavioral effects of these drugs. Inherent in the formation of these hypotheses is the premise that other, nonmotoric behavioral consequences of neuroleptic administration, such as changes in arousal (Beninger 1982) or the hedonic impact of rewards (Wise et al. 1978), are better correlated with clinical efficacy. Response changes indicative of drug-induced alterations in these processes are typically observed at doses subthreshold for motor or performance impairment.

A majority of studies designed to test neuroleptic effects on spontaneous motor activity in laboratory animals have employed photocell measures. When administered to rats in doses approximating those used therapeutically, haloperidol does not appear to impair activity in this procedure (Costall et al. 1983), whereas crossovers in an open field environment are significantly reduced (Schaefer and Michael 1984; Hard et al. 1985). Although it is not uncommon for drug effects to vary with the apparatus, closer examination in our laboratory has revealed significant haloperidol-induced reductions in photocell activity during the later portion of a test session (Figure 1a). Interestingly, this same pattern of decline in locomotor responses over time has also been observed for rearing and crossing in an open field (Figure 1, b and c), where the response function is even more pronounced. Examination of control response patterns in saline-injected rats reveals a gradual decline of mean response rates over five 2-min intervals in the photocell chamber; this pattern is conspicuously absent in the open field, where controls rear and cross steadily over the 10-min session. Therefore, it appears that this dose of haloperidol induces a significant habituation of responding in both experimental situations, but that this pattern is less readily discernable when testing is conducted in the enclosed, darkened photocell chambers with white noise presented (where control animals habituate quickly).

These studies indicate that spontaneous motor activity may be a useful behavior for studying low-dose neuroleptic effects if within-session data are examined. Thus, although overall session totals may fail to reveal significant behavioral changes induced by these antipsychotic agents (as was the case for both procedures employed here), subtle differences in temporal patterns of responding may be detected. Furthermore, as drug-treated rats responded at saline levels during the initial portion of the test sessions, subsequent habituation may reflect a neuroleptic-induced attenuation of arousal or attention to environmental stimuli. This finding, in conjunction with the observation that saline-injected animals do display a similar habituation when retested in the open field environment (unpublished observation), indicates that (within-session) temporal patterns of responding may be related to neuroleptic-enhanced filtering of irrelevant sensory information in psychotic states.

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