Biochemical Pharmacology, Vol. 27, pp. 1729–1730.

0006-2952/78/0701-1707/$02.00/0

COMMENTARY

PHENYLETHYLAMINE AND BRAIN FUNCTION*

HECTOR C. SABELLI
Rush-Presbyterian St. Luke's Hospital, Chicago, IL, U.S.A.
and
RICHARD L. BORISON, BRUCE I. DIAMOND and HENRI S. HAVDALA
Mt. Sinai Hospital Medical Center, Chicago, IL, U.S.A.†
and
NEDATHUR NARASIMHACHARI
Illinois State Psychiatric Institute, Chicago, IL, U.S.A.

Central adrenergic pathways appear to be the neural mechanism for arousal, excitement and elation. The notion that catecholamines (CA) are the main and only central adrenergic mediators is held against the evidence that the behavioral effects of exogenously administered CA are mainly depressant [1]. Since nonhydroxylated phenylethylamines are behavioral stimulants, we proposed in 1966 that 2-phenylethylamine (PEA), an amphetamine-like metabolite of phenylalanine, may be responsible for many of the "ergotropic" functions usually attributed to brain CA [2–5]. Endogenous PEA has been identified in human [6] and other mammalian brains [3, 4, 7] and in many peripheral tissues [8]. Since we have recently reviewed [9, 10] animal and clinical studies on PEA, in this paper we will only focus on their possible biological and medical significance; to this end, some speculative hypotheses for which there is limited experimental evidence but which may have heuristic value for future research will be discussed.

Brain content and metabolism

Brain PEA originates in part from the *in situ* decarboxylation of L-phenylalanine [9, 11] and in part from the uptake of blood-borne PEA [11, 12]; the latter accounts for the ability of the peripheral decarboxylase inhibitor, carbidopa [12], and the peripheral monoamine oxidase inhibitor (MAOI), dimethyl-beta-carbolinium iodide [13], to markedly modify the brain PEA content.

The subcellular distribution, brain regional distribution and metabolism of PEA are not entirely known. PEA is hydroxylated by dopamine-beta-hydroxylase forming phenylethanolamine, a neuroamine identified by mass and infrared spectroscopy in brain [14] and by enzymatic assay in brain and peripheral tissues [15]. The most important route for disposition is monoamine oxidase (MAO); in fact, PEA is extremely sensitive to this enzyme, especially type B MAO for which it is the preferential endogenous substrate [15, 16]. Unless MAO is inhibited, the effects of administered PEA are fleeting. In a similar manner, MAO must be rapidly inactivated during extraction; otherwise, PEA is rapidly destroyed and measurements of tissue PEA content may give inaccurately low values.

There has been considerable uncertainty regarding the PEA content of biological samples [3, 4, 7, 12, 17–20]. In spite of severe discrepancies regarding the brain content of PEA, values for MAOI-treated animals measured by different methods are fairly similar. It should be noted that, when a low brain PEA content has been measured, a 1000-fold increase has been observed after MAOI [7, 18] whereas when a high PEA content was measured, only a 3 to 4-fold increase [3, 20] was observed, in agreement with results obtained with exogenous labeled PEA [21]. We have now measured PEA as its isothiocyanate derivative using gas–liquid chromatography and gas–liquid chromatography–mass spectrometry;‡ these two methods are highly specific and sensitive (400 pg) and showed agreement within 10 per cent. With these methods, we have essentially confirmed our previous observations; rabbit whole brain contains 236 ± 23 ng/g of PEA, a concentration similar to that of CA. Lower values have been found in rat brain [7, 17, 18, and R. L. Borison, unpublished results]. Efficient extraction with simultaneous inactivation of MAO was obtained by rapid homogenization of fresh ice-cold brain samples in a benzene–sodium hydroxide–pargyline mixture. Recovery was measured using tritiated PEA as internal standard; deuterated phenylethylamines are known to be much less sensitive to MAO than their natural analogs [22], a fact which may contribute to the low values obtained using deuterated PEA as internal standard.

Mode of action

The administration of PEA induces amphetamine-like central stimulation (electroencephalographic-alerting, increased exploration and motor activity, anti-convulsant, etc.) and peripheral sympathomimetic signs. Only the latter appear to be entirely due to CA release, since they can be prevented by reserpine. PEA releases CA also in brain [23] but such release appears to account for only part of its central effects. Thus, the administration of PEA but not that

* Previously unpublished research supported by the Department of Anesthesiology Research Fund.
† Address to which reprints are to be sent.
‡ R. L. Borison, N. Narasimhachari, P. J. Maple, H. S. Havdala and H. C. Sabelli, presented to *Soc. Biol. Psychiat.*, San Francisco, CA, June 10–13, 1976.

of DOPA mimics the actions of amphetamine on evoked potentials and exploratory behavior [2, 5]. Further, alpha-methyl-*p*-tyrosine does not prevent many of the behavioral effects of PEA [24] (although it blocks similar behavioral actions induced by amphetamine and reduces some of the extra-pyramidal effects of PEA).

Other central effects of PEA may be mediated by its metabolites: phenylethanolamine, a weak stimulant with unusual proconvulsant effects (shortening of maximal electroshock seizure latency) [25]; phenylacetaldehyde, the MAO product of PEA, which produces sedation [26]; and phenylacetic acid.* Most of the behavioral stimulant effects of PEA are enhanced (or not altered) by inhibitors of MAO [2, 5] or of dopamine-beta-hydroxylase [25]; thus, they appear to be exerted by PEA itself. This suggests that specific receptors for this amine must exist; they have not been as yet conclusively demonstrated, but indirect evidence for their presence has been obtained in brain cortex [27], spinal cord [28] and pancreas [29].

PEA and affective disorders

Pharmacological studies have suggested that endogenous depression is due to a deficit of brain phenylethylamines, whereas antidepressive drug actions, elation and mania may result from an increase in their turnover. Although catecholamines have been widely implicated, the behavioral depressant effect of injected CA, the failure of L-DOPA and of cocaine (a norepinephrine reuptake inhibitor) in the treatment of depression and the lack of effect of tricyclic antidepressants on brain CA levels indicate that CA cannot be the only phenylethylamines which regulate affective behavior. PEA has been shown at least indirectly to satisfy the four main criteria required to demonstrate that a neuroamine sustains mood and that its deficit can be responsible for depression. First, ability to induce behavioral stimulation: PEA is unique among naturally occurring amines in exerting amphetamine-like effects. Second, decrease in amine turnover associated with depression and, conversely, an increase with mania: in 1968, Fischer *et al.* [30] reported drastically diminished urinary excretion of PEA in a group of patients with endogenous depression; this finding has been corroborated by every laboratory in which it was studied [4, 20, 31–33] in spite of the difficulties in quantifying PEA. In contrast, depressions secondary to schizophrenia or exogenous (situational) depressions show normal or high PEA urinary excretion. PEA deficit is often found in acute psychotic depressions (monopolar or bipolar) as well as in many chronic "neurotic" depressions; since the rate of PEA excretion in these patients is outside the range found in normals, the test may have diagnostic value. Isolated measurements of the 24-hr urinary excretion of PEA in manic patients [32] suggest that PEA turnover may be increased in these subjects. These clinical studies must be repeated using more specific methods for PEA determinations. Using gas chromatography of the isothiocyanate derivative of PEA, we found† that control subjects excrete in 24 hr $61.2 \pm 12.8\,\mu g$ of free PEA and 53.2 ± 12.0 ng of conjugated PEA/g of creatinine. Third, antidepressant effect of the amine or its amino acid precursor: phenylalanine (particularly the D isomer) has been shown to exert antidepressant effects [32, 34–36]. D-Phenylalanine increases the brain content of PEA [20], but it is not known whether it is decarboxylated to PEA or if it acts indirectly. In contrast, the amino acid precursors for CA and serotonin exert only weak antidepressant effects in a limited number of depressed subjects. Fourth, brain levels and/or turnover are decreased by drugs which cause depression and enhanced by euphoriant and stimulant agents: PEA urinary excretion in humans and PEA brain levels and metabolism in animals are decreased by reserpine [3, 4] and by alphamethyldopa [12], whereas they are increased by marihuana [37, 38], alcohol [24], amphetamines [12, 39], and antidepressive treatments such as imipramine [3, 20], MAOI [20] and electroshock [40]. (Amitriptyline, which is effective in imipramine-resistant depressions, has not as yet been studied.) Treatment with MAOI or imipramine-like antidepressants raises PEA urinary excretion in depressed subjects in parallel with clinical improvement [32]. In animals, imipramine-like agents markedly increase (4-fold) brain content [2, 3] and synthesis [10] of PEA, whereas they do not affect the brain content of other neuroamines. In addition, they inhibit MAO [41], particularly type B [42]. The most effective antidepressants among classical MAO inhibitors, such as tranylcypromine and pargyline [43], also preferentially inhibit MAO type B. Furthermore, a new and potent clinical antidepressant‡ deprenyl, is a specific type B MAO inhibitor and affects only the metabolism of PEA [43]. In contrast, selective inhibitors of type A MAO (which metabolizes CA and serotonin) are devoid of antidepressant effects. According to most investigators, the antidepressant effect of MAO inhibitors is due to CA accumulation whereas their hypotensive effect is due to relative CA deficit resulting from the accumulation of "false neurotransmitters." In our view, both effects are due to the increased levels of non-catecholic neuromodulators (e.g. PEA and phenylethanolamine) which have stronger behavioral effects and weaker cardiovascular actions than CA [24].

The antimanic agent haloperidol blocks the central effect of PEA in mice [44]. Chronic treatment with lithium markedly decreases PEA synthesis, a phenomenon which may account for the antimanic effect of this cation.§ Lithium also markedly decreases PEA disposition. The prophylactic effect of lithium against both mania and depression can also be related to its effects upon PEA metabolism in animals. Thus, chronic lithium treatment prevents the "depressant" effect of reserpine as well as the "manic" effect of amphetamine in mice, and it also prevents the effects of reserpine and of amphetamine upon PEA synthesis and metabolism.§

* U. P. Madubuike, A. D. Mosnaim and H. C. Sabelli, presented to the *XXVI Int. Congr. Physio. Sci.*, New Delhi, India, Oct. 20–26, 1974.

† R. L. Borison, N. Narasimhachari, P. J. Maple, H. S. Havdala and H. C. Sabelli, presented to *Soc. Biol. Psychiat.*, San Francisco, CA, June 10–13, 1976.

‡ L. Tringer, G. Haits and E. Varga, presented to the *V Conf. Hung. Pro Therap. et Investig. in Pharmac.* (1971).

§ R. L. Borison, H. C. Sabelli, B. I. Diamond, P. Maple and H. S. Havdala, presented to the *Soc. Neurosci.*, Toronto, Canada, Nov. 7–11, 1976.

The PEA theory of affective disorders [2, 5, 40] has an important implication for the psychotherapy of depression. The demonstrations that certain forms of depression are associated with a deficit in PEA and that replacement therapy with phenylalanine can relieve such depression lead us to believe that endogenous depression is not primarily an emotional disorder but rather a metabolic disease characterized primarily by psychiatric symptomatology. Hence, antidepressant drug therapy is an indirect (pharmacological) "replacement" of brain PEA rather than purely symptomatic; in fact, tricyclics do not elevate mood in situational depressions or in normals. Since the patient's lack of insight into the metabolic nature of his intrapsychic and interpersonal conflicts results in the development of a secondary neurosis which may be self-perpetuating, we now provide the neuroamine theory of depression to the patient as the core of psychotherapy.

Drug abuse

Alcohol, marihuana, opioids and amphetamines, agents commonly abused because of their euphoriant effects, have been shown to increase the brain content and/or turnover of PEA. We have recently found [12, 39] that amphetaminic drugs (including methylphenidate) first decrease (to 30 per cent of control with D-amphetamine, 0.5 mg/kg) and subsequently increase markedly the brain levels of endogenous PEA; concomitantly, PEA synthesis is increased and disposition is accelerated [24]. Further, the PEA depleter, carbidopa, partially prevents the central effects of D-amphetamine [12]. These observations, together with the close structural and pharmacological similarities between amphetamine and PEA, support the view that the central actions of amphetamine may be mediated in part by release and increased synthesis of endogenous PEA.

The brain levels of PEA are increased in animals approximately 4-fold by the mood-elevating agents alcohol [24] and delta-9 tetrahydrocannabinol (THC) [37, 38]. The euphoriant effect of THC appears to be mediated by endogenous PEA: its behavioral stimulant actions are enhanced by PEA, by MAOI, and by CA depletion; further, THC inhibits the disposition of exogenous PEA, enhances the excitatory effects of microiontophoretic administration of PEA to cortical neurons and potentiates the behavioral stimulant effects of systemically administered PEA [28, 37]. No experimental studies with opioids have as yet been published but Inwang *et al.* reported [45] marked alterations in PEA urinary excretion during withdrawal from opioid addiction in man. One may speculate that alcoholism and drug abuse, which are often observed in affective disorders, may be attempts at self-medication.

PEA in other brain disorders

The urinary output of PEA is reduced in Parkinsonian patients [44]; a deficiency in brain PEA may explain the depressive symptoms often found in these subjects. The low PEA excretion in Parkinsonism, the clinical anti-Parkinson effect of phenylalanine [35], the high concentration of endogenous PEA in striatum [11], and the ability of PEA to induce choreic-like movements in animals, to potentiate the central nervous system stimulant effects of DOPA and to antagonize the reserpine-induced Parkinson-like syndrome in mice suggest that PEA may also play a role in extrapyramidal functions. We have observed that L-DOPA increases the brain content [44] and the synthesis (R. L. Borison, unpublished results) of PEA in mouse brain; also benztropine and trihexyphenidyl increase PEA synthesis in brain (R. L. Borison, unpublished results).

The urinary excretion of PEA has also been studied in schizophrenia by Fischer *et al.* [4, 32]. Although a marked heterogeneity in the patient's pattern of excretion was noted [32], these results have aroused the interest of other investigators who have speculated on the role of PEA in schizophrenia [46].

The genetic deficiency in phenylalanine hydroxylase in phenylketonuria leads to excessive formation (and increased urinary excretion) of phenylalanine metabolites including PEA [47, 48], phenylacetic acid (which we have shown* to be formed in brain mainly via PEA rather than via phenylpyruvic acid) and a neurotoxic Schiff base formed by PEA and pyridoxal phosphate [49]. Animal studies [50] suggest that such PEA excess may contribute to the behavioral disorder observed in these patients. Conversely, the therapeutic effectiveness of methylphenidate and amphetamine in minimal brain dysfunction suggests that PEA may be one of the neuroamines whose deficit is suspected to underlie this syndrome.

As does tyramine, the parenteral administration of PEA causes severe migraine headaches (E. Fischer, unpublished results). This observation, together with the ability of MAOI to prevent some forms of migraine, leads us to speculate that the deaminated metabolites of PEA and other neuroamines may be implicated in this disorder. In contrast, Sandler *et al.* [51] has speculated that a decrease in PEA metabolism may contribute to the physiopathology of migraine.

PEA and anesthetic agents

Further evidence for the role of PEA in alerting mechanisms has been obtained in studies with anesthetic agents in mice.† Whereas the administration of DOPA actually potentiates pentobarbital-induced anesthesia, the administration of PEA markedly shortens it. Further, the recovery from brain tissue of injected ^{14}C-labeled PEA is increased by anesthetic doses of ethanol (833 per cent of control), halothane (434 per cent) and pentobarbital (128 per cent). Recovery of labeled PEA after the administration of labeled phenylalanine is increased to a lesser extent by ethanol (408 per cent) and by halothane (165 per cent) and to a greater extent by pentobarbital (411 per cent). These results are consistent with pre-synaptic inhibition of PEA release by pentobarbital and with decreased turnover or metabolism of brain PEA after the administration of halothane or ethanol.

* U. P. Madubuike, A. D. Mosnaim and H. C. Sabelli, presented to the *XXVI Int. Congr. Physio. Sci.*, New Delhi, India, Oct. 20–26, 1974.

† H. S. Havdala, R. L. Borison, P. J. Maple, H. C. Sabelli and B. I. Diamond, presented to the *Am. Soc. Anesthesiol.*, San Francisco, CA, Oct. 11–14, 1976.

PEA as a neuromodulator

The above studies suggest that PEA plays an important role in the modulation of wakefulness, arousal, affect, extrapyramidal movement and other functions known to be influenced by endogenous CA. Because PEA is the only endogenous amine, which, when administered, increases exploratory behavior and produces the selective changes in cortical evoked potential induced by alerting stimuli [5], we have proposed that PEA is a major mediator for the reticular activating system responsible for behavioral and electroencephalographic arousal [2]. Thus, PEA would serve as the humoral substrate for attention [10].

It should not be surprising that PEA and CA also play a role in the modulation of affect. The work of Magoun on Reticular Activating mechanisms, as well as the classical contributions of Pavlov on the Orienting Reflex, indicates that attention is one of the basic drives which underlies basic (e.g. exploratory behavior) as well as complex patterns of behavior. Human affect appears to be based in part on attentive functions; depressed patients characteristically have a deficit in attention which may account for their lack of care for themselves as well as for others.

The actual cellular mechanism of PEA action is as yet unknown. Because PEA can be formed in CA neurons and because it freely crosses the blood–brain barrier [11], it is unlikely that it functions as a true synaptic transmitter. The concept of neuromodulator has been widely discussed; we have recently attempted to define it [52] by Dale's principle. Whereas in its initial formulation, it was postulated that only one transmitter was released, we proposed [52] that each neuron releases only one type of chemically related modulators. Because the various membranes, organelles and enzymatic mechanisms involved in the synthesis, storage and release of chemical messengers act preferentially on certain substrates rather than others, a neuron synthesizes and releases mainly one transmitter. However, because the specificity of the enzymatic and non-enzymatic mechanisms required for the synthesis, storage and release of the main transmitter is not absolute, a neuron may also form and release other metabolically related substances. Thus, for CA transmitter, the corresponding neuromodulators might include the amine analogues formed as by-products of CA synthesis, such as PEA as well as the metabolites of the amines. Zeller *et al.* [53] have shown that PEA may actually be a co-transmitter for norepinephrine in the sympathetic nerve endings innervating the iris. We speculate that PEA also serves in the brain as a co-transmitter which sustains and modifies the action of CA. Thus, a deficit in PEA would shorten the ergotropic effect of pleasurable stimuli [10] and weaken the homeostatic neuroamine mechanisms which restore euthymia when mood is lowered by depressogenic stimuli [32].

Although future research is likely to discard many of these hypotheses, there is sufficient experimental evidence to pursue the study of the role of PEA in brain function.

REFERENCES

1. E. Marley, *Pharmac. Rev.* **18,** 753 (1966).
2. E. Fischer, R. I. Ludmer and H. C. Sabelli, *Acta physiol. Latinoam.* **17,** 15 (1967).
3. H. C. Sabelli, W. J. Giardina, A. D. Mosnaim and N. H. Sabelli, *Acta physiol pol.* **24,** 33 (1973).
4. E. Fischer, H. Spatz, B. Heller and H. Reggiani, *Experientia* **28,** 307 (1972).
5. H. C. Sabelli and W. J. Giardina, in *Chemical Modulation of Brain Function* (H. C. Sabelli), p. 225. Raven Press, New York (1973).
6. E. E. Inwang, A. D. Mosnaim and H. C. Sabelli, *J. Neurochem.* **20,** 1469 (1973).
7. D. A. Durden, S. R. Philips and A. A. Boulton, *Can. J. Biochem.* **51,** 995 (1973).
8. D. M. Jackson and D. M. Temple, *Comp. gen. Pharmac.* **1,** 155 (1970).
9. H. C. Sabelli, A. D. Mosnaim and A. J. Vazquez, in *Adv. Behav. Biol.* (Eds. R. R. Drucker-Colin and R. D. Myers), p. 10. Plenum, New York (1974).
10. H. C. Sabelli, R. L. Borison, B. I. Diamond, J. May and H. S. Havdala, in *Phenylethylamine: Biological Mechanisms and Clinical Aspects* (Eds. A. D. Mosnaim and M. E. Wolf). Marcel Dekker, New York, (1978).
11. T. Nakajima, Y. Kakimoto and I. Sano, *J. Pharm. exp. Ther.* **143,** 319 (1964).
12. R. L. Borison, A. D. Mosnaim and H. C. Sabelli, *Life Sci.* **14,** 1837 (1974).
13. R. L. Borison, H. C. Sabelli and B. Ho, *Pharmacologist* **17,** 258 (1975).
14. A. D. Mosnaim, E. E. Inwang, J. H. Sugarman, W. J. DeMartini and H. C. Sabelli, *Biol. Psychiat.* **6,** 235 (1973).
15. J. M. Saavedra and J. Axelrod, *Proc. natn. Acad. Sci., U.S.A.* **70,** 769 (1973).
16. R. F. Squires, *Adv. Biochem. Psychopharm.* **5,** 355 (1972).
17. J. Willner, H. F. Lefevre and E. Costa, *J. Neurochem.* **23,** 857 (1974).
18. J. M. Saavedra, *J. Neurochem.* **22,** 211 (1974).
19. J. W. Schweitzer, A. J. Friedhoff and R. Schwartz, *Biol. Psychiat.* **10,** 277 (1975).
20. A. D. Mosnaim, E. E. Inwang and H. C. Sabelli, *Biol. Psychiat.* **8,** 227 (1974).
21. H. Y. T. Yang and N. H. Neff, *J. Pharmac. exp. Ther.* **187,** 365 (1973).
22. B. Belleau, J. Burba, M. Pindell and J. Reiffenstein, *Science, N.Y.* **133,** 102 (1961).
23. K. Fuxe, H. Grobecker and J. Jonson, *Eur. J. Pharmac.* **2,** 202 (1967).
24. H. C. Sabelli and R. L. Borison, *Adv. Biochem. Psychopharmacology* (Ed. E. Costa), Vol. 15, p. 69. Raven Press, New York (1976).
25. H. C. Sabelli, A. J. Vazquez and D. F. Flavin, *Psychopharmacologia* **42,** 117 (1975).
26. H. C. Sabelli and W. J. Giardina, *Biol. Psychiat.* **2,** 119 (1970).
27. W. J. Giardina, W. A. Pedemonte and H. C. Sabelli, *Life Sci.* **12,** 153 (1973).
28. W. R. Martin and C. G. Eades, *Pharmacologist* **16,** 205 (1974).
29. J. M. Feldman and H. E. Lebovitz, *J. Pharmac. exp. Ther.* **179,** 56 (1971).
30. E. Fischer, B. Heller and A. N. Miro, *Arzneimittel-Forsch.* **18,** 1486 (1968).
31. A. A. Boulton and L. Milward, *J. Chromat.* **57,** 287 (1971).
32. E. Fischer, *Biol. Psychiat.* **10,** 667 (1975).
33. H. Spatz and N. Spatz, in *Phenylethylamine: Biological Mechanisms and Clinical Aspects* (Eds. A. D. Mosnaim and M. E. Wolf). Marcel Dekker, New York, (1978).
34. E. Fischer, B. Heller, N. Nachon and H. Spatz, *Arzneimittel-Forsch.* **25,** 132 (1975).
35. B. Heller, in *Phenylethylamine: Biological Mechanisms*

and Clinical Aspects (Eds. A. D. Mosnaim and M. E. Wolf), Marcel Dekker, New York, (1978).
36. H. Spatz, B. Heller, M. Nachon and E. Fischer, *Biol. Psychiat.* **10,** 235 (1975).
37. H. C. Sabelli, A. J. Vazquez, A. D. Mosnaim and L. Madrid-Pedemonte, *Nature, Lond.* **248,** 144 (1974).
38. H. C. Sabelli, W. A. Pedemonte, C. Whalley, A. D. Mosnaim and A. J. Vazquez, *Life Sci.* **14,** 149 (1974).
39. R. L. Borison, A. D. Mosnaim and H. C. Sabelli, *Life Sci.* **17,** 1331 (1975).
40. H. C. Sabelli and A. D. Mosnaim, *Am. J. Psychiat.* **131,** 695 (1974).
41. S. Gabay, in *Phenylethylamine: Biological Mechanisms and Clinical Aspects* (Eds. A. D. Mosnaim and M. E. Wolf), Marcel Dekker, New York, (1978).
42. J. A. Roth and C. N. Gillis, *Biochem. Pharmac.* **23,** 2537 (1974).
43. C. Braestrup, H. Andersen and A. Randrup, *Eur. J. Pharmac.* **34,** 181 (1975).
44. H. C. Sabelli, A. D. Mosnaim, R. L. Borison and M. E. Wolf, in *Drugs and Central Synaptic Transmission* (Eds. B. N. Dhawan and P. B. Bradley), MacMillan, New York, (1977).
45. E. E. Inwang, B. J. Primm, F. L. Jones, H. Dekirmenjian, J. M. Davis and C. T. Henderson, *Drug Alcohol Dependence,* **1,** 295 (1976).
46. M. Sandler and G. R. Reynolds, *Lancet* **1,** 70 (1976).
47. J. B. Jepson, W. Lovenberg and P. Zaltman, *J. Biochem. Tokyo* **74,** 5 (1960).
48. J. A. Oates, P. Z. Nirenberg, J. B. Jepson, A. Sjoerdsma and S. Udenfriend, *Proc. Soc. exp. Biol. Med.* **112,** 1078 (1963).
49. Y. M. Loo, *J. Neurochem.* **14,** 813 (1967).
50. D. J. Edwards and K. Blau, *Analyt. Biochem.* **45,** 387 (1972).
51. M. Sandler, M. B. H. Youdim and E. A. Hanington, *Nature, Lond.* **250,** 335 (1974).
52. H. C. Sabelli, A. D. Mosnaim, A. J. Vazquez, W. J. Giardina, R. L. Borison and W. A. Pedemonte, *Biol. Psychiat.* **11,** 481 (1976).
53. E. A. Zeller, A. D. Mosnaim, R. L. Borison and S. V. Huprikar, in *Advances in Biochemical Psychopharmacology* (Eds. E. Giacobini, E. Costa and R. Paoletti). Raven Press, New York (1976).