Cerebral Synaptic Transmission and Behavioral Effects of Dimethoxyphenylethylamine: A Potential Psychotogen

Abstract. *Dimethoxyphenylethylamine, like mescaline which it resembles, impairs cerebral synaptic transmission and behavior in cats. It has properties associated with hallucinogens and, on this score, qualifies as a potential inducer of psychosis. The idea of such an endogenous inducer is thus reaffirmed by the candidacy of dimethoxyphenylethylamine.*

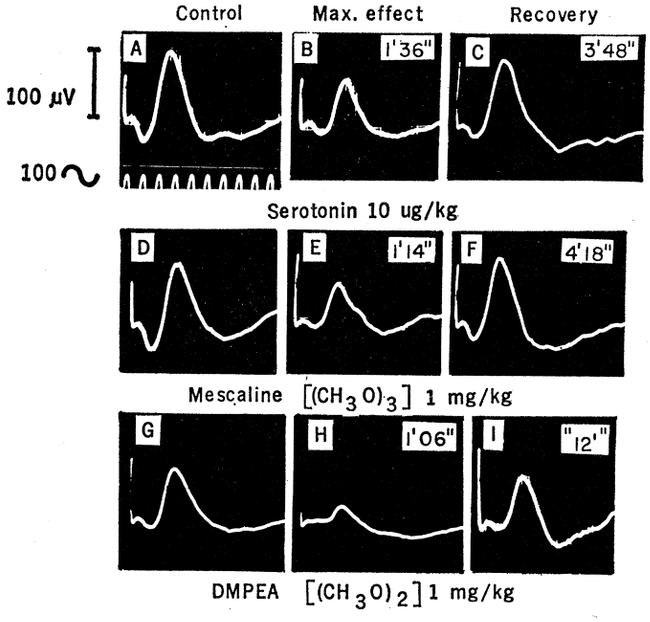
The compound 3,4-dimethoxyphenylethylamine (DMPEA), a possible metabolite of cerebral dihydroxyphenylethylamine (dopamine), has been reported (*1–4*) in large amounts in the urine of some schizophrenics as well as of some patients with Parkinson's disease (*5*). There is not, as yet, unanimity on the urinary findings or on their interpretation (*4, 6*). Nevertheless, the findings have caused reasonable speculation on the role that endogenous DMPEA, originating from a possible "error of metabolism," might play in the production of the symptoms of some forms of mental disturbance. Conversion of dopamine to DMPEA has indeed been reported (*2, 7*), although Kuehl *et al.* in their subsequent work were unable to show urinary DMPEA in one patient given dihydroxyphenylalanine (dopa) (*8*).

Another approach to assessing the significance of the findings awaiting validation is the use of experimental animals to examine the characteristic, relevant effects of this potential inducer of psychosis or psychotogen. Among the most relevant of such tests are the effects on cerebral synaptic transmission (*9*) and on quantitative behavior (*10*). Thus we have shown that catechol and indolamine hallucinogens disturb cerebral synaptic transmission by impeding it and that a behavioral counterpart is found in increased latency of response, in decreased discrimination, and in release phenomena in the rat, cat, dog, and monkey (*11*). In man there are corresponding changes in the electrical activity of the cerebrum and in perception measurements (*11*). Furthermore, the specificity of the synaptic and behavioral effects of these drugs is attested to by their susceptibility to antagonism by chlorpromazine (*12, 13*).

Therefore, we decided to determine whether DMPEA, qualified structurally by being a close analog of the hallucinogen mescaline, which differs from DMPEA by having an additional methoxy group in the ring, also qualifies by having the synaptic and behavioral properties of the latter. As with mescaline and lysergic acid diethylamide (LSD), we used postsynaptic cortical potentials that were transcallosally evoked to monitor cerebral synaptic transmission initiated by a constant submaximal impulse every 2 seconds in a cat lightly anesthetized with pentobarbital (*12*); and conditioned differentiation between a correct (2-kc) tone (a response to which is rewarded with milk) and an incorrect (1-kc) tone in the cat to quantify behavior (*13*).

Indeed, DMPEA does have the same kind of action as mescaline and is even more potent, while both are less active than serotonin in the same experiment (Fig. 1). Chlorpromazine, in doses that have no apparent influence on transmission per se, prevents or markedly reduces all of these effects.

The graph of response latencies (Fig. 2) illustrates that administration of DMPEA produces a prolongation of the delay in response that is greatly increased if the drug, which has been given intraperitoneally, is protected from destruction by previous treatment of the animal with a monoamine oxi-



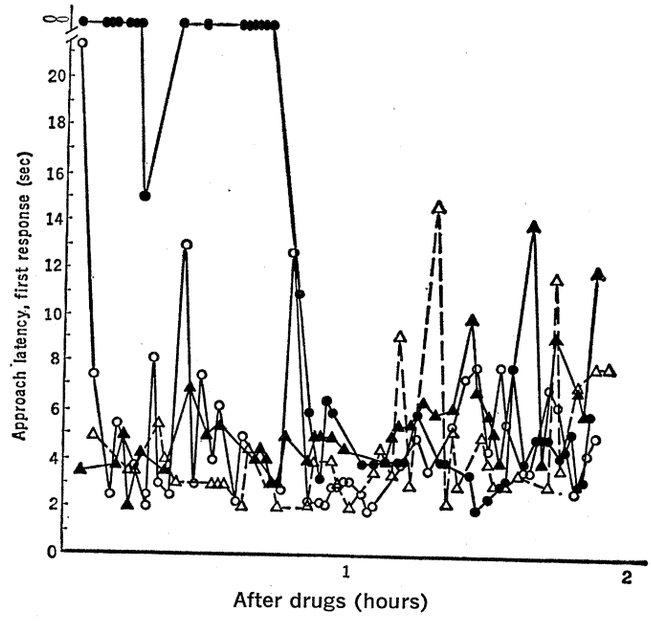


Fig. 1 (left). Comparative cerebral synaptic inhibitory action of methoxyphenylethylamines. Transcallosally evoked cortical potentials; submaximal stimuli every 2 seconds. Ipsilateral common carotid injections in cat treated with pentobarbital; 1 mg of mescaline is equivalent to 10 μg of serotonin; 1 mg of DMPEA is equivalent to 18 μg of serotonin. Fig. 2 (right). Increase of DMPEA inhibition in cat by iproniazid. Differential approach for milk. Stimuli at 50-second intervals; duration, 22 seconds. Solid circles, DMPEA with the monoamine oxidase inhibitor; open circles, DMPEA alone (6 mg per kilogram of body weight); solid triangles, monoamine oxidase inhibitor (2 mg per day per kilogram of body weight, × 2); open triangles, saline.

dase inhibitor (iproniazid). The oxidative deamination catalyzed by monoamine oxidase (MAO) does not play as prominent a part in experiments on cerebral synaptic transmission, because here the DMPEA is given by close-arterial injection, thus reducing exposure to the MAO *before* the DMPEA reaches the site of action. Hence, increasing the number of methoxy groups in the ring, that is, masking the hydroxy by converting them to methoxy groups, reduces cerebral synaptic activity and, in contrast, reduces vulnerability to destruction by oxidative deamination. Thus, the resultant effect is influenced by several opposing factors such as the two mentioned.

In the case of LSD, which showed similar impairment of cerebral synaptic function and of behavior in our animal experiments (*11, 12*), we also measured the impairment of human behavior resulting from synaptic inhibition, which we have shown in animals to be most marked in an area involved in visual association (*14*), with an objective visual perception test. This test shows that a perceptual dissociation can be induced in schizophrenics by subclinical doses of LSD which have no effect on the normal controls (*15*). This sensitive quantitative test may reveal behavioral changes in humans where other investigators (*16*) have been unable to do so by gross observation in an unstated number of subjects given DMPEA orally. This last-mentioned report suggested that more trials should be conducted with amine destruction reduced by MAO inhibitors. Similarly, depending on gross observation, two other groups (*17*) could not detect changes in a small number of volunteers given higher doses but no MAO inhibitors.

The qualitative identity of the cerebral synaptic and behavioral actions of the structurally similar DMPEA (*18*) and mescaline supports the possibility that endogenous DMPEA is a potential inducer of psychosis.

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Terminals of Single Ia Fibers: Distribution within a Pool of 300 Homonymous Motor Neurons

Abstract. *The excitatory postsynaptic potentials produced in motoneurons by impulses in single afferent fibers (Ia) have been recorded with the aid of an averaging computer. These responses were used to map the distribution of the terminals of single fibers within the pool of 300 motoneurons of the medial gastrocnemius muscle. Twelve Ia fibers were studied in separate experiments. Monosynaptic excitatory postsynaptic potentials were found in 94 percent of the 77 motoneurons investigated. This finding indicates that each of the 300 motoneurons must receive afferent fibers from almost all of the spindles of the muscle it innervates.*

Recent studies (*1*) on stretch reflexes have raised questions regarding the organization of input to motoneurons. The afferent fibers from primary spindle receptors in skeletal muscle make direct connections with motoneurons which innervate the muscle of origin (*2*), but the precise distribution of the afferent terminals within the pool of motoneurons has never been established. Limitations in existing anatomical techniques make it difficult to follow all the axonal ramifications of a single neuron in the central nervous system, especially if the branches are widely distributed. In particular, the number of motoneurons receiving terminals from a single afferent fiber and the spatial extent of the terminal branching are unknown. We explored several approaches to this problem before adopting the one described below. In brief, we have recorded the excitatory postsynaptic potentials (EPSP's) produced in gastrocnemius motoneurons of the cat by impulses in a single afferent fiber (Ia) from that muscle. We have used these responses to map the distribution of the Ia terminals among the approximately 300 motoneurons of this muscle. Since these EPSP's are very small, an averaging computer was used to extract the signals from the baseline noise.

Two types of experiments, differing slightly, were carried out on cats anesthetized with sodium pentobarbital. In both, all of the hindlimb nerves were cut, except for the nerve supplying the medial gastrocnemius muscle. Some of the branches of this nerve were also severed, reducing the sensory input from the medial gastrocnemius to about one third of normal. The dorsal roots through which this remaining input was channeled were repeatedly subdivided and tested until a rootlet was found which yielded electrical records meeting all criteria (*3*) for identification of discharges from a single group Ia fiber. All other dorsal roots from lumbar 6 through sacral 2 were then cut so that the afferent connections of the medial gastrocnemius were finally reduced to a single group Ia fiber. Using 3- to 5-megohm micropipettes filled with 3*M* KCl, we made intracellular recordings of the EPSP's produced in medial gastrocnemius motoneurons by impulses in this fiber when the intact branch of the nerve to this muscle was stimulated electrically. An averaging computer (CAT 400B) was used to summate a large number of individual EPSP's and