distinguishable from that produced by amphetamine. Ephedrine was selected for this study because it is a widely used sympathomimetic amine which, we thought, had not been abused and could therefore serve as a negative control in validating the methods. Review of the literature revealed several case reports of the abuse of ephedrine. Panse[20] in his review cites two cases of ephedrine abuse reported by Groenewald in his dissertation in medicine (Dusseldorf, 1960). Subsequently, Herridge and A'Brook[12] reported two cases and Prokop[22] one case of ephedrine abuse. In these cases there was not only evidence of compulsive drug-seeking behavior, but all patients developed a toxic schizophrenia-like psychosis. It would thus appear that the constellation of subjective and physiological responses herein described provides a valid measure of the abuse potentiality of amphetamine-like drugs.

Epinephrine was the only catecholamine whose excretion was enhanced by the five sympathomimetic agents studied. The blood pressure changes are more characteristic of those produced by norepinephrine than epinephrine. These findings would be consistent with Vane's[24] observation and conclusions that the pressor effect of tyramine and amphetamine is caused by a local tissue release of norepinephrine which is not accompanied by an increase in circulatory norepinephrine. The observations in man are difficult to reconcile with the observations of Harvey and associates[10] who found that amphetamine increased blood norepinephrine levels in the anesthesized pithed cat with or without adrenal glands. It is possible that dose level and route of administration may be important differences between the experiments. In Harvey's and associates' study, all doses were administered intravenously, while in our study they were administered subcutaneously. Further, the lowest dose of amphetamine that they studied was 0.5 mg. per kilogram whereas, in the study in man it was 30 mg. per 70 Kg. It is quite certain that the peak levels of amphetamine obtained in this study would be less than those obtained in Harvey's and associates' study. Of course, species differences may also be of importance.

Studies of Thomä and Wick[23] indicate that phenmetrazine is a directly acting sympathomimetic amine since its pressor effect and effect on the nictitating membrane were enhanced rather than antagonized by cocaine. The fact that phenmetrazine enhanced epinephrine excretion in man would therefore suggest that increased activity of the adrenal gland was due to the central activation of efferent sympathetic fibers. There is little evidence that methylphenidate causes the release of either epinephrine or norepinephrine from peripheral sympathetic neurons or that it has a significant direct sympathomimetic action[18, 19]; therefore, it must be assumed that the peripheral autonomic changes must be a consequence of a central action of methylphenidate. One must further assume on the basis of methylphenidate's peripheral effects that either the central norepinephrine receptors differ from those in the periphery or that methylphenidate interacts with another type of receptor.

If this line of reasoning is correct, and it is based on the assumption that the pharmacology of these agents elucidated in animals is applicable to man, and one further assumes that the similarity of the syndromes of the five amines indicates that they have a similar mode of action, then one must conclude that the euphorogenic and psychotogenic effects of these agents must be due to activation of a receptor other than a noradrenergic receptor; however, these data do not completely rule out the noradrenergic hypothesis because methylphenidate may inhibit the uptake of centrally released norepinephrine since it has other cocaine-like activity[18, 19] and therefore could increase the amount of norepinephrine available at central postsynaptic receptors.

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