

Sedative-like Effect of Epinephrine

A Review

PETER ROGER BREGGIN, MD, SYRACUSE, NY

WHEN FELDBERG and Sherwood demonstrated that intraventricular injections of epinephrine (Adrenaline) in dogs caused "sedative-like" behavioral depression, they suggested that epinephrine secretion during anxiety in humans might cause analogous symptoms of fatigue and somnolence.¹⁸ Little or no attention was subsequently given this hypothesis; Feldberg himself did not mention it in his recent (1963) book about the pharmacology of the brain.¹⁷ The hypothesis has received little attention for two reasons: first, there has been little evidence that *systemic* epinephrine could reach the brain, and second, there has been little or no evidence that *systemically* administered epinephrine could produce sedative-like or fatigue-like effects.

Both these objections have been modified by recent experimental findings. First, radioactively tagged epinephrine has been shown to cross the blood-brain barrier in the region of the hypothalamus during sustained systemic infusions,^{1,45} and second, epinephrine has been shown to cause sedative-like effects during sustained systemic injections.^{6,39} These and other recent findings have created a need for a review of the literature concerning epinephrine-induced behavioral depression, and for an evaluation of possible mechanisms and clinical implications.

I. Sedative-Like Effects With Epinephrine

Sharpless produced what he called "stupification" in cats with sustained intravenous infusions of relatively small amounts of epinephrine.³⁹ He found that 2 μ g/kg/minute

Submitted for publication Sept 25, 1964.

State University of New York, Upstate Medical Center. Resident and Assistant Instructor, Department of Psychiatry, 1964; Massachusetts Mental Health Center, Resident in Psychiatry; and Harvard Medical School, Teaching Fellow in Psychiatry, 1963-1964.

Reprint requests to 342 Roosevelt Ave, Syracuse, NY 13210.

for 30 minutes produced a decrement in approach behavior, while larger doses produced sleep. The behavior was associated with a "drowsy" electroencephalograph pattern. The effect was also similar to that produced by direct instillation of epinephrine into the brain.³⁹

My interest in the behavioral depressant properties of epinephrine began independently with the discovery that intramuscular injections of epinephrine in oil produced sedative-like effects in rats.⁶ In a pilot study it was found that relatively large doses (100 μ g) completely abolished hunger-motivated approach behavior. In this same range (50 μ g-100 μ g) dose-dependent behavioral changes were produced in 15-30 minutes and lasted for several hours. The obvious changes included somnolence, sluggishness, loss of muscular tonus, and relative unresponsiveness to various stimuli, including loud noises, jolts, and toe pinching. Smaller doses did not produce obvious behavioral changes. However, smaller doses (10 μ g-40 μ g) produced a statistically significant, dose-dependent reduction in exploratory behavior in a 6-foot runway. The effect seemed independent of the peripheral autonomic response as measured by heart rate: doses in this range (15 μ g-25 μ g) had little or no effect on heart rate as recorded under nonstressful conditions by chronically implanted electrocardiograph electrodes. The behavioral effects were probably caused by relatively low systemic blood levels of the drug, since the absorption of epinephrine in oil from the muscles is delayed over a period of several hours or more. For example, with large doses (100 μ g) a pronounced acceleration of heart rate was still obvious more than two hours after injection in all four animals injected.

In addition to the above two studies in which relatively small, prolonged systemic doses were used, other studies have demonstrated decremental effects upon behavior with larger single doses of epinephrine in dogs³⁰ and birds.^{12,19}

Key studied the effects of single systemic injections of epinephrine upon young chickens before and after the maturation of their blood-brain barrier.²⁹ In 1-28-day-old chicks (before the maturation of the blood brain barrier) he produced behavioral depression or sleep and slow wave EEG activity with both epinephrine and levarterenol (Norepinephrine); he found the changes "identical to those produced by the central depressant, pentobarbitol sodium." In more mature 4-week-old chicks he produced a mixed arousal and depressant response, and in still older chicks (after the maturation of the blood brain barrier) he produced only arousal. He hypothesized that epinephrine given before the development of the blood-brain barrier had the same effect as epinephrine given directly into the brain of mature animals. Such a clear-cut distinction between depression and arousal may have been achieved because he used single injections of epinephrine; other experiments, as already noted, subsequently demonstrated sedative-like effects in mature rats and cats with prolonged systemic doses.^{6,39}

There has been much more thorough and well-known documentation for sedative-like effects following the direct instillation of epinephrine into the central nervous system.^{3,18,25,31,35,38} Feldberg and Sherwood, for example, described in detail a response "indistinguishable from that of a light sodium pentobarbitone anaesthesia,"¹⁸ which closely resembles the response to systemic injection.^{6,29,39}

II. Possible Mechanisms of Action

These studies strongly suggest that the sedative-like effect of systemic epinephrine is central in origin. First, there is a great similarity between the animal's delayed response to sustained systemic infusion and the animal's more immediate response to direct CNS injection. The relative impermeability of the blood-brain barrier to epinephrine may account for the delay during systemic infusion. Second, single systemic injections can cause depression in chicks before but not after the maturation of the blood-brain barrier. In addition, a number of effects of systemic epinephrine can be reproduced by direct instillation into the brain, eg, increased respiratory rate³⁷ and general analgesia.^{8,28} Finally, there is some supportive

evidence that the behavioral depression is independent of peripheral autonomic changes as measured by heart rate and blood pressure following both the systemic administration^{6,19} and the central nervous system administration of epinephrine.^{30,31}

For systemic epinephrine to have a direct effect upon the brain, it must cross the blood-brain barrier. Large intravenous doses of epinephrine increased the level of epinephrine in the cerebral spinal fluid, and consistent with the sedative-like effect, the increase did not become apparent for 30-60 minutes.¹⁶

Several investigators have demonstrated a perceptible amount of levarterenol and epinephrine in the cerebrospinal fluid under relatively normal conditions,^{32,41,44} while Draskoci found, in one coincidental observation, that the cerebral spinal fluid epinephrine level increased during a simultaneous rise in the circulating systemic epinephrine.¹⁶ Studies using radioactively tagged epinephrine have also demonstrated that systemically administered epinephrine can cross the blood-brain barrier.^{1,45} None was detected after two minutes, but an appreciable amount was detected in the hypothalamus after 30 minutes. This, too, is consistent with the delayed sedative-like effect following systemic administration. Since the radioactively tagged epinephrine was found only in the hypothalamus, and since the hypothalamus is known to influence sedation,^{8,27} the plausibility is increased for a direct action of systemic epinephrine upon the central nervous system.

An alternative mechanism is possible for any sedative-like effect of *endogenous* epinephrine secretion. Vogt has demonstrated that epinephrine secretion from the adrenal medulla is accompanied by a depletion of epinephrine within the hypothalamus.⁴² This depletion might represent a release of epinephrine stores in the hypothalamus leading to an increase of epinephrine in the cerebrospinal fluid or to a redistribution of epinephrine within the hypothalamus itself. This would mimic those experiments dealing with the direct instillation of epinephrine into the brain. Consistent with this, Domer and Feldberg have shown that dye injected into the ventricles can cross into the hypothalamus.¹⁵

III. Application to Human Psychophysiology

The data concerning epinephrine-induced sedative-like effects in humans is sparse. Few studies have set out to measure any possible sedative-like effect following small, prolonged doses of epinephrine in humans. The extrapolation from behavioral depression in animals to symptoms of fatigue and sedation in humans must be made with caution.

There are some incidental notations in the literature that individuals given prolonged intravenous injections report symptoms of sedation or fatigue.^{2,9,10,34} Basowitz, for example, produced such symptoms, apparently in a mild form, with as little as $5\mu\text{g}/\text{kg}/\text{hour}$.² However, in similar studies these symptoms have not been mentioned²⁶ or have been found absent.²⁰ The experimental results concerning systemically administered epinephrine in humans are thus equivocal, but suggestive.

In one experiment the direct instillation of epinephrine into the central nervous system of a human (a single subject was given 2 mg of epinephrine intracisternally) produced a deep sleep documented on the electroencephalograph.³¹

There is no controlled data concerning sedation or fatigue in humans in response to endogenous secretions of epinephrine. However, it has been noted clinically that individuals who are persistently or intensely anxious, and who presumably have high blood levels of epinephrine, often complain of sedative-like or fatigue-like symptoms.^{13,33,40} It is also frequently reported by athletes and other "normal" subjects that they feel very tired while anxiously awaiting some stressful event.

Breggin has described a model for the psychophysiology of anxiety which includes the sedative-like effect of epinephrine.⁵ The model draws upon Hess' hypothesis that the hypothalamus has two competing or antagonistic functions, the ergotropic which controls arousal and sympathotonia, and the trophotropic which controls sedation and parasympathotonia.²⁷ This present paper has reviewed evidence that epinephrine, secreted during arousal can cause sedative-like effects. There is also evidence that epinephrine can cause delayed, compensatory parasympathetic activation in humans.⁵ Thus epinephrine secreted during ergotropic activation of the hypothalamus may act as a hormonal feedback to

the hypothalamus to produce compensatory trophotropic activation.⁵ This physiological model would parallel the clinical observations of Misch who noted that anxiety occurs in two stages: an initial acute response characterized by arousal and sympathomimetic symptoms (Hess' ergotropic activation) and a delayed response characterized by fatigue-like and parasympathomimetic symptoms (Hess' trophotropic activation).³³ An epinephrine feedback mechanism might account for many of the unstable and fluctuating symptoms of persistent, intense anxiety.

Comment

In any discussion of the sedative-like effect of epinephrine it is necessary to account for the paradoxical arousal and anxiety-inducing effects of epinephrine in humans. For some time it has been thought that epinephrine can produce an arousal effect upon human and animal electroencephalograms, and perhaps upon behavior. Rothballer³⁶ and Dell¹⁴ have both reviewed the literature pertaining to these effects. The evidence is not at variance with data concerning the sedative-like effect. First, studies demonstrating an arousal effect have used only single doses, and have produced only fleeting changes in the EEG. Second, the studies of arousal in humans have been equivocal and contradictory,^{11,14,21-24,36} while studies of animals have been clear-cut only when the brains have been sectioned.^{4,14,36} In his review of the literature, Dell summarized, "... it is unlikely that an injection of adrenaline in a normal awake animal or man would give rise to clear-cut changes in behavior."¹⁴

While epinephrine injection may or may not produce some amount of arousal in the awake human subject, it can produce clinically apparent anxiety. Many studies have demonstrated that epinephrine can elicit anxiety in certain individuals under specific experimental conditions.⁵ The acute anxiety response is immediate, presumably before any appreciable amount of epinephrine could cross the blood-brain barrier. Most likely, the acute anxiety response to epinephrine is a learned or conditioned response to the sympathomimetic symptoms evoked by the epinephrine.⁵ This may account for the self-generating nature of anxiety, since the symptoms of anxiety can act as cues which further reinforce the anxiety. However, this learned response is not incompatible with the

sedative-like response which is more delayed, and which probably results from a direct physiological action.

This discussion of the sedative-like effect of epinephrine has been entirely limited to physiological responses. However, I have no intention of oversimplifying the very complex problem of symptom-formation during stress. While epinephrine may initiate sedative-like or fatigue-like symptoms, purely psychological factors may enhance or diminish these symptoms. Psychological responses may initiate the secretion of epinephrine, and psychological responses may be keyed off by the symptoms produced by epinephrine. Purely physiological considerations reflect a very limited aspect of the individual's total behavior, though for practical purposes these considerations may at times be made in relative isolation from the remainder of the individual's behavior.

In conclusion, the concept of epinephrine-induced sedative-like effects gives direction to further experimental and clinical research. First, the exact nature of the central nervous system depression requires clarification. Most studies have indicated that the effect is in part soporific. However, other components must be ruled out, such as tranquilization, psychomotor retardation on a neuromuscular basis, and general analgesia. It is also possible that an affective or "emotional" response is involved, such as "panic" or psychomotor retardation on a psychological basis. Second, the capacity of *endogenous* epinephrine to produce symptoms of fatigue or somnolence during persistent anxiety needs investigation. Third, the extrapolation from animal studies to human clinical experiences must be bridged by further research. Finally, many clinically important subtleties must be investigated. For example, there may be variation in the permeability of the blood-brain barrier within the same individual or among different individuals. Similarly, there may be variation in epinephrine output in response to anxiety, or there may be variation in the sensitivity of the central nervous system to epinephrine.

Summary

Several experiments have now demonstrated a sedative-like or fatigue-like effect following the systemic injection of epinephrine in animals. These effects have been comparable to those

previously described following the direct instillation of epinephrine into the central nervous system. Sedative-like and fatigue-like symptoms have been noted incidentally after epinephrine injections in humans, but this finding has been inconstant and has not been subjected to rigorous study. However, it is well known that these symptoms are reported during persistent anxiety, which is presumably characterized by a high output of epinephrine.

The following hypothesis was offered: epinephrine secreted from the adrenal medulla during persistent anxiety can act as a hormonal feedback to the hypothalamus, resulting in compensatory sedative-like and fatigue-like symptoms. Supporting evidence for this hypothesis was reviewed, and further areas of research were suggested.

Generic and Trade Names of Drugs

Levarterenol bitartrate—Levophed Bitartrate.

REFERENCES

1. Axelrod, J. H.; Weil-Malherbe, H.; and Tomchick, R.: Physiological Distribution of H³-Adrenaline and Its Principle Metabolite, Metanephrine, *Fed Proc* 18:364, 1959.
2. Basowitz, H., et al: Anxiety and Performance Changes With Minimal Dose of Epinephrine, *AMA Arch Neurol Psychiat* 76:98-106, 1956.
3. Bass, A.: Über eine Wirkung des Adrenalins auf das Gehirn, *Z Ges Neurol Psychiat* 26:600-601, 1914, cited by Draskoci et al.¹⁰
4. Bonvallet, M.; Dell, P.; and Hiebel, G.: Tonus Sympathetique et activité électrique corticale, *Electroenceph Clin Neurophysiol* 6:119-144, 1954, cited by Rothballer.²⁰
5. Breggin, P.: Psychophysiology of Anxiety With Review of Literature Concerning Adrenaline, *J Nerv Ment Dis*, to be published.
6. Breggin, P.: Psychophysiology of Arousal and Fear of Arousal, unpublished Thesis in partial fulfillment of the degree of Doctor of Medicine, Western Reserve University, Cleveland, June, 1962.
7. Brodic, B.; Spector, S.; and Shore, P. S.: Interaction of Drugs With Norepinephrine in Brain, *Pharmacol Rev* 11:548-556, 1959.
8. Buscaino, V. M., and Pero, C.: *Rass Clin Ther* 21:691, 1940, cited Leimdorfer et al.²¹
9. Cameron, D. E.: Adrenalin Administration in Resistant Anxiety States, *Amer J Med Sci* 210:281-288, 1945.
10. Cameron, D. E.: Further Studies in Use of Adrenalin in Treatment of Resistant Anxiety States, *Psychiat Quart* 20:425-433, 1946.
11. Cardon, P. V., et al: Physiological and Psychological Effects of Intravenously Administered Epine-

- phrine and Its Metabolism in Normal and Schizophrenic Men: I, *J Psychiat Res* 1:37-49, 1961.
12. Clymer, N. V., and Seifter, J.: Method of Screening Sympathomimetic Amines for Stimulant Action on Cerebrum, *J Pharmacol Exp Ther* 89:149-152, 1947.
 13. Cohen, M. E., and White, P. D.: "Life Situations, Emotions and Neurocirculatory Asthenia (Anxiety Neuroses, Neuresthenia, Effort Syndrome)," in *Life Stress and Bodily Disease*, H. R. Wolff, ed., Baltimore: William & Wilkins Co., 1950.
 14. Dell, P.: "Intervention of Adrenergic Mechanism During Brain Stem Reticular Activation," in *CIBA Symposium on Adrenergic Mechanisms*, J. R. Vane, G. E. W. Walstenholme, and M. O'Connor, ed., Boston: Little Brown, & Co., 1960.
 15. Domer, F., and Feldberg, W.: "Some Central Actions of Adrenaline and Noradrenaline When Administered into Cerebral Ventricles," in *CIBA Symposium on Adrenergic Mechanisms*, J. R. Vane, G. E. W. Walstenholme, and M. O'Connor, Boston: Little Brown & Co., 1960.
 16. Draskoci, M.; Feldberg, W.; Haranath, P. S. R. K.: Passage of Circulating Adrenaline Into Perfused Cerebral Ventricles and Subarachnoid Space, *J Physiol* 150:34-49, 1960.
 17. Feldberg, W.: *Pharmacological Approach to Brain From Its Inner and Outer Surface*, Baltimore: Williams & Wilkins Co., 1963.
 18. Feldberg, W., and Sherwood, S. L.: Injections of Drugs Into Lateral Ventricle of Cat, *J Physiol (London)* 123:148-167, 1954.
 19. Frank, M. M., et al: Behavioral Effects of Epinephrine and Norepinephrine, *Fed Proc* 18:390, 1959.
 20. Frankenhauser, M., and Jarpe, G.: Psychophysiological Changes During Infusions of Adrenalin in Various Doses, *Psychopharmacologia (Berlin)* 4: 424-432, 1963.
 21. Gibbs, F. A., and Maltby, G. L.: Effect on Electrical Activity of Cortex of Certain Depressant and Stimulant Drugs—Barbituates, Morphine, Caffeine, Benzedrine, and Adrenalin, *J Pharmacol* 78:1-10, 1943.
 22. Gottschalk, L.: Effect of Epinephrine on Cortical and Basal Electroencephalograms and Eosinophile Count, *Arch Neurol Psychiat* 67:522-534, 1952.
 23. Greenblatt, M., et al: Electroencephalographic Patterns From Base of Brain, *Amer J Psychiat* 103: 749-757, 1947.
 24. Grinker, R. R., and Serota, H. M.: Electroencephalographic Studies of Corticohypothalamic Relations in Schizophrenia, *Amer J Psychiat* 98:385-392, 1941.
 25. Haley, T. J., and McCormick, W. G.: Pharmacological Effects Produced by Intracerebral Injections of Drugs in Conscious Mouse, *Brit J Pharmacol* 12:12-15, 1957.
 26. Hawkins, D. R., et al: Psychological and Physiological Responses to Continuous Epinephrine Infusion, *Psychiat Res Rep Amer Psychiat Assoc* 12:40-52, 1960.
 27. Hess, W. R.: *Diencephalon, Autonomic and Extrapyramidal Functions*, New York: Grune and Stratton, 1954.
 28. Ivy, A., et al: Analgesic Effect of Intracardial and Intravenous Injection of Epinephrine in Dogs and Subcutaneous Injection in Man, *Quart Bull Northwest Univ Med Sch* 18:298-306, 1944.
 29. Key, B. J., and Marley, E.: Effect of Some Sympathomimetic Amines on Behavior and Electro-cortical Activity of Chicken, *Electroenceph Clin Neurophysiol* 14:90-105, 1962.
 30. Leimdorfer, A.: Action of Sympathomimetic Amines on Central Nervous System and Blood Sugar: Relation of Chemical Structure to Mechanism of Action, *J Pharmacol Exp Therap* 98:62-71, 1950.
 31. Leimdorfer, A.; Arana, R.; and Hack, M. A.: Hyperglycemia Induced by Action of Adrenaline on Central Nervous System, *Amer J Physiol* 150:588-595, 1947.
 32. Manger, W. M., et al: Epinephrine and Arterenol (Norepinephrine) in Mental Disease, *AMA Arch Neurol Psychiat* 78:396-412, 1957.
 33. Misch, W.: Syndrome of Neurotic Anxiety; Somatic and Psychic Components of Its Genesis and Therapy, *J Ment Sci* 81:389-414, 1935.
 34. Pollin, W., and Goldin, S.: Physiological and Psychological Effects of Intravenously Administered Epinephrine and Its Metabolism in Normal and Schizophrenic Men: II. Psychiatric Observations, *J Psychiat Res* 1:50-66, 1961.
 35. Reitter, H.: Narkoseffekt durch intrazisternale Adrenalin Injection, *Der Anaesthetist*, 6:131-135, 1957, cited by Draskoci et al.¹⁶
 36. Rothballer, A. B.: Studies of Adrenaline-Sensitive Components of Reticular Activating System, *Electroenceph Clin Neurophysiol* 8:603-621, 1956.
 37. Rothballer, A. B.: Effect of Catecholamines on Central Nervous System, *Pharmacol Rev* 11:494-544, 1959.
 38. Rothballer, A. B., and Sharpless, S. K.: Unpublished data, cited in Sharpless.³⁹
 39. Sharpless, S. K.: Effects of Intravenous Infusions of Epinephrine and Norepinephrine on Conditioned Reflex in Cat, *Psychopharmacologia (Berlin)* 1:140-149, 1959.
 40. Tompkins, E. H.; Sturgis, C. C.; and Wearn, J. T., *Studies in Epinephrine: II*. *Arch Intern Med* 24:269-283, 1919.
 41. Vogt, M.: Concentration of Sympathin in Different Parts of Central Nervous System Under Normal Conditions and After Administration of Drugs, *J Physiol* 123:451-481, 1954.
 42. Vogt, M.: Catecholamines in Brain, *Pharmacol Rev* 11:483-494, 1959.
 43. Vogt, M.: "'Chairman's Opening Remarks' for Session 7: Central Adrenergic Mechanisms," in *CIBA Symposium on Adrenergic Mechanisms*, J. R. Vane, G. E. W. Walstenholme, and M. O'Connor, ed., Boston: Little Brown & Co., 1960.
 44. Weil-Malherbe, H., and Liddel, D. W.: Adrenaline and Noradrenaline in Cerebrospinal Fluid, *J Neurol* 17:247-249, 1954.
 45. Weil-Malherbe, H.; Axelrod, J.; and Tomchick, R.: Blood Brain Barrier for Adrenalin, *Science*, 129: 1226-1227, 1959.