Central Serotonergic Agents Raise the Repetitive Extrasystole Threshold of the Vulnerable Period of the Canine Ventricular Myocardium

CHARLES M. BLATT, STEPHEN H. RABINOWITZ, AND BERNARD LOWN

SUMMARY Systemic administration of three central serotonergic agents, melatonin, 5-methoxytryptophol, and 6-chloro-2-(1-piperazinyl)-pyrazine (MK-212), produced significant increases in the threshold of the vulnerable period for repetitive electrical activity in the canine cardiac ventricle. MK-212 was effective despite bilateral vagotomy. The specific serotonin antagonist, metergoline, blocked the effect of MK-212 on the threshold. An increase in central serotonergic activity may inhibit the flow of arrhythmogenic sympathetic nerve traffic from the brain to the heart.

THE ROLE of sympathetic nervous activity in predisposing to diverse cardiac arrhythmias already had been delineated early in this century (Hunt, 1899; Garrey, 1908; Rothberger and Winterberg, 1911; Levy, 1913). Although such neural traffic is centrally mediated (Beattie et al., 1930; Dikshit, 1934), most investigations have focused on the peripheral sympathetic system innervating the heart. If arrhythmias are to be controlled and prevented by interventions aimed at modifying neural cardiac traffic, blunting the genesis of such impulses at their source within the brain is an attractive challenge.

Several reports suggest that central sympathetic neural outflow can be inhibited by neuropharmacological measures that purportedly increase levels of the biogenic amine, serotonin, in the central nervous system (Antonaccio and Robson, 1973, 1975; Baum and Shropshire, 1975). Rabinowitz and Lown (1978) have demonstrated that the administration to anesthetized dogs of a biochemical precursor of serotonin, together with enzyme-inhibiting agents that favor the formation and accumulation of serotonin in the brain, raises the threshold of the vulnerable period for repetitive ventricular response and diminishes cardiac susceptibility to ventricular fibrillation. The aim of the present investigation was to identify chemical and endogenous compounds that act through the central serotonin system to raise the cardiac threshold without the assistance of enzyme inhibitors and to learn more about the mechanism of their action. Since administration of pineal gland hormone, melatonin, increases brain serotonin (Anton-Tay et al., 1968), it was relevant to examine its action on cardiac vulnerability, as well as effects of related compounds, namely, 5-methoxytryptophol and 6-chloro-2-(1-piperazinyl)-pyrazine (MK-212, Merck) (Clineschmidt et al., 1977).

Cardiac vulnerability was evaluated in both conscious and anesthetized dogs by the repetitive extrasystole method developed in this laboratory (Rabinowitz et al., 1976; Matta et al., 1976). To detect the presence of a serotonergic mechanism mediating the effect of MK-212 on the threshold, the specific serotonin antagonist metergoline was employed. MK-212 also was tested in vagotomized animals to exclude the possibility of vagal mediation of the effect on the threshold.

Methods

General

Healthy mongrel dogs of either sex, weighing between 10 and 20 kg and at least 1 year old, were studied. Food but not water was withheld from dogs for 18 hours before study. Experiments were always initiated between 9 and 10:00 a.m. The dogs were exposed to a normal diurnal variation of light and dark. Two or 3 days before conscious animals were studied, catheters for cardiac electrical testing were introduced into the right ventricle under sterile conditions while the dogs were anesthetized with the short-acting drug thiamylal sodium (Surital,
Parke-Davis), 50 mg/kg, administered intravenously. Catheters were introduced at the beginning of experiments in anesthetized dogs.

Cardiac Electrical Testing

A Medtronic no. 6901 bipolar catheter was employed for cardiac electrical testing and cardiac pacing. A unipolar catheter (Elecath) recorded the right ventricular endocardial electrogram. These two catheters were bound together side by side with silk sutures. Guided by fluoroscopic visualization, the combined catheter assembly was passed through a jugular vein and positioned at the apex of the right ventricle.

Cardiac Pacing

The distal pole of the pacing catheter was made cathodal. Pacing was accomplished with a rectangular waveform 2 msec in duration. The current intensity of the pacing stimulus was set at twice the mid-diastolic threshold for a propagated response. The hearts were paced at a cycle length of 333 msec, corresponding to a heart rate of 180 beats/min.

Repetitive Extrasystole Threshold Determination

The threshold current for evoking more than one response (a repetitive extrasystole) to a single stimulus served as a measure for susceptibility to ventricular fibrillation (Fig. 1). A testing cycle of 5 seconds was used to determine the repetitive extrasystole threshold. Each cycle consisted of 4 seconds of cardiac pacing followed by delivery of the test impulse, and then 1 second for observing the response. The test pulse was a rectangular pulse of 5-msec duration and 2-ma intensity delivered in mid-diastole. For anesthetized dogs, the pulse duration was shortened to 2 msec. In successive cycles, the test stimulus was delivered progressively earlier in diastole in 5-msec steps until the boundary of the refractory period was encountered. When scanning of the vulnerable period of the cardiac cycle was completed without encountering a repetitive extrasystole, the intensity of the test stimulus was increased by 2 ma and the procedure was repeated. The repetitive extrasystole threshold was taken as the minimum current intensity at which a single stimulus evoked a repetitive extrasystole in two of three trials.

Melatonin Administration

Melatonin, N-acetyl-5-methoxytryptamine (Sigma Chemical) in crystalline form, was dissolved (10 mg/ml) in a solvent of 40% ethanol (95%) in normal saline. Melatonin was administered intravenously to six anesthetized and 13 conscious dogs in a dose of 10 mg/kg. To assess the effect of the melatonin solvent on the repetitive extrasystole threshold, five conscious and four anesthetized dogs received an intravenous bolus of ethanol (1 ml/kg) in normal saline solution. Heart rate and repetitive extrasystole threshold were noted before and at 30-minute intervals for 360 minutes after injection of melatonin and its solvent.

Ethyl alcohol levels were determined on samples of blood drawn from a forelimb vein before and at specified intervals after injections of either the melatonin dissolved in ethanol or the ethanolic vehicle alone. Quantitative measurement of ethanol in serum was performed with Calbiochem ethyl alcohol reagents. The procedure developed by Calbiochem was employed (U.S. patent 3,926,736).

5-Methoxytryptophol Administration

5-Methoxytryptophol (Sigma Chemical), a compound naturally occurring in the pineal gland and closely related to melatonin, was dissolved (10 mg/ml) in 40% ethanol (95%) in normal saline. The resulting solution was administered to four conscious dogs as an intravenous bolus in a dose of 5 mg/kg. Heart rate and repetitive extrasystole threshold were noted both before and at 30-minute intervals for 180 minutes after injection of this compound.

MK-212 and Metergoline Administration

6-Chloro-2-(1-piperazinyl)-pyrazine (MK-212, Merck), a central serotonin-mimetic agent chemically unrelated to melatonin, was used to elucidate...
the mechanism of the action of melatonin. MK-212 (0.1 mg/ml) was dissolved in normal saline. The resulting solution was administered intravenously to eight conscious dogs in a dose of 0.1 mg/kg of body weight. Heart rate and repetitive extrasystole threshold were noted both before and at 30-minute intervals for 180 minutes after injection of this compound.

To test the hypothesis that the effect of MK-212 on the repetitive extrasystole threshold is mediated by a serotonin receptor, metergoline (Farmitalia), 1 mg/kg, was administered intravenously to 12 conscious dogs. Metergoline is a selective antagonist of serotonin that acts within the central nervous system, as well as in the periphery (Sastry and Phillis, 1977). The metergoline was dissolved in 10 ml of distilled water containing 250 mg of l-ascorbic acid (Nutritional Biochemicals). Six of the 12 dogs served as a control group. Heart rate and repetitive extrasystole threshold were noted before and at 30-minute intervals for 240 minutes after the injection of metergoline. In the remaining six animals, MK-212, 0.1 mg/kg, was given intravenously 120 minutes after metergoline. Heart rate and repetitive extrasystole threshold were noted before and at 30-minute intervals for 120 minutes after MK-212 had been injected.

Administration of MK-212 after Vagotomy

To determine whether intact vagus nerves are necessary for the action of MK-212 on the repetitive extrasystole threshold, 12 anesthetized dogs were used. The cervical vagosympathetic trunks were sectioned bilaterally 2 cm below the level of the carotid bifurcation. After a 30-minute rest period, the repetitive extrasystole threshold was determined. The heart rate was maintained constant at 214 beats/min (pacing stimuli delivered at 280-msec intervals) during the threshold testing. This rate was chosen to ensure the ability to override rapid spontaneous rates encountered after vagotomy. In five of the 12 dogs, MK-212, 0.1 mg/kg, was administered intravenously. In the remaining seven animals, MK-212, 0.2 mg/kg, was injected. The repetitive extrasystole threshold was determined every 30 minutes for 90 minutes. After each threshold measurement the spontaneous (unpaced) heart rate was noted.

Experimental Protocol

Anesthetized Dogs

The dogs were anesthetized with alpha-chloralose, 100 mg/kg, iv. Supplemental anesthesia was administered at 50 mg/kg as required. The vagotomized dogs were an exception and were anesthetized with intravenous pentobarbital, 30 mg/kg. Ventilation was accomplished through a cuffed endotracheal tube attached to a Harvard constant volume pump respirator. Sufficient oxygen was added to room air to maintain arterial Po₂ in the range of 90-150 mm Hg. The respiratory rate was set at 14/min and the tidal volume was adjusted to maintain arterial pH in the range of 7.35-7.45. Abdominal systolic pressure was determined by a large lumen stiff-walled cannula inserted through a right femoral arteriotomy and connected to a Statham 231D pressure transducer and amplifier. A meter display of the mean arterial pressure was obtained by electrically integrating the phasic amplifier output. The system was calibrated against a mercury manometer. Rectal temperature was measured with an electronic thermometer (Yellow Springs Instruments) and maintained in the range of 37-39.5°C with thermal blankets. The ECG was recorded from a unipolar right ventricular endocardiative lead and monitored continuously by oscilloscope. A femoral vein was cannulated for intravenous administration of chemical solutions. The repetitive extrasystole threshold, heart rate, and blood pressure were determined in six dogs treated with melatonin. Thresholds also were determined in four dogs treated only with the solvent for melatonin, and in 12 bilaterally vagotomized animals injected with MK-212.

Conscious Dogs

On the day of the study, dogs were placed into a ventilated cage in a quiet room. After a 1-hour adaptation period, repetitive extrasystole thresholds were determined in 13 dogs before and after a melatonin injection. Threshold determinations also were made in five dogs injected with the solvent for melatonin, in four injected with 5-methoxytryptophol, and in 14 injected with MK-212.

The results were analyzed using the appropriate Student's t-test (double-tailed) for independent or for paired data, by linear regression where indicated in the text, and by a randomized complete block analysis of variance on the Tektronix 31 programmable calculator.

Results

Effects of Melatonin on the Repetitive Extrasystole Threshold, Heart Rate, and Mean Arterial Pressure

In six anesthetized dogs, the repetitive extrasystole threshold increased from 20 ± 2 ma (mean ± SEM) to 30 ± 3 ma (P = 0.002) 90 minutes after the intravenous administration of melatonin, 10 mg/kg (Fig. 2). The repetitive extrasystole threshold remained elevated for 360 minutes of observation, attaining a maximum of 34 ± 4 ma 300 minutes after melatonin injection. The mean arterial pressure remained essentially unchanged at about 130 mm Hg during the period of observation. A reduction of approximately 25% from an initial heart rate of 163 ± 13 beats/min was demonstrated by an analysis of variance to be statistically significant (P < 0.05), and correlated inversely (r = -0.85, P < 0.001) with the repetitive extrasystole threshold.
Anesthetized Dogs

PERCENT CHANGE IN REPETITIVE EXTRASYSTOLE THRESHOLD

FIGURE 2 The effect of melatonin on the repetitive extrasystole threshold, heart rate, and blood pressure in six anesthetized dogs. Analysis of variance demonstrated a significant (P < 0.01) increase in threshold and a significant decrease (P < 0.05) in heart rate with no change in blood pressure after injection. Vertical lines represent mean ± SEM.

That is to say, as the threshold increased, the spontaneous or unpaced heart rate decreased (Fig. 3).

In 13 conscious dogs, sitting quietly in a cage, the repetitive extrasystole threshold increased from 23 ± 2 to 29.5 ± 2 ma (P = 0.0002) 150 minutes after the intravenous injection of melatonin, 10 mg/kg (Fig. 4). The increase in repetitive extrasystole threshold was sustained during 210 minutes of observation. The initial heart rate of 105 ± 7 beats/min decreased by about 10% (P < 0.05) during the experiment, and this slight bradycardia correlated well (r = -0.84, P < 0.05) with the increase in the threshold.

Effects of Ethanol on the Repetitive Extrasystole Threshold

To factor out effects of ethanol on the repetitive extrasystole threshold, four anesthetized and five conscious dogs (Table 1) were injected with the ethanolic solvent (1 ml/kg) used as a vehicle for melatonin. No significant change in repetitive extrasystole threshold occurred during 210 minutes of observation. In seven conscious dogs, 45 minutes after the injection of the solvent, the venous blood ethanol level was 50 ± 6 mg/dl. This level in humans would represent a lower limit of mild intoxication.

Figure 4 Percent changes in the repetitive extrasystole threshold in conscious animals after injection of various central serotonergic agents: (1) melatonin, 10 mg/kg, in 13 dogs; (2) methoxytryptophol, 5 mg/kg, in four dogs; (3) MK-212, 0.1 mg/kg, in eight dogs. Vertical lines represent the mean ± SEM. Analysis of variance demonstrated significant (P < 0.05) changes in threshold with each drug.

Effects of Ethanol on the Repetitive Extrasystole Threshold

Table 1 Changes in the Repetitive Extrasystole Threshold in Conscious Dogs 90 Minutes after Injection

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of dogs</th>
<th>Mean ± SEM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melatonin in ethanol</td>
<td>13</td>
<td>+25 ± 9%</td>
<td>0.002</td>
</tr>
<tr>
<td>Methoxytryptophol</td>
<td>4</td>
<td>+22 ± 12</td>
<td>0.04</td>
</tr>
<tr>
<td>Ethanol solution</td>
<td>5</td>
<td>-2 ± 15</td>
<td>0.80</td>
</tr>
<tr>
<td>MK-212 in saline</td>
<td>8</td>
<td>+34 ± 12</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Effects of 5-Methoxytryptophol on the Repetitive Extrasystole Threshold

In four conscious dogs, sitting quietly in a cage, the repetitive extrasystole threshold increased from 28 ± 2 to 34 ± 3 ma (P = 0.04) 90 minutes after an intravenous injection of 5-methoxytryptophol, 5 mg/kg. At 150 minutes after the injection, the threshold returned to the control level (Fig. 4). No significant change from the initial heart rate of 110 ± 15 beats/min occurred during the experiment.

Effects of MK-212 on the Repetitive Extrasystole Threshold

In each of eight dogs sitting quietly in a cage, the repetitive extrasystole threshold increased from 31.5 ± 4 to 42 ± 4 ma (P = 0.02) 90 minutes after MK-212 administration (Fig. 4). The repetitive extrasystole threshold remained elevated for 240 minutes after MK-212 injection. The heart rate decreased by about 10% from an initial value of 112 ± 5 beats/min (P < 0.05) and correlated inversely (r = −0.77, P < 0.05) with the threshold.

In six dogs serving as a control group, the repetitive extrasystole threshold ranged from 28 ± 2 to 31 ± 3 ma during 240 minutes of observation after the administration of the centrally active serotonin-blocking agent, metergoline. Analyses of variance disclosed no significant change in the threshold or in the heart rate, that initially was 119 beats/min. In six additional dogs, 120 minutes after the administration of metergoline, the repetitive extrasystole threshold was 29 ± 2 ma and the heart rate was 113 ± 10 beats/min. MK-212 then was given. No significant change occurred in the repetitive extrasystole threshold (Fig. 5) or the heart rate during the subsequent 120 minutes.

Effects of MK-212 after Vagotomy

Twelve anesthetized and bilaterally vagotomized dogs were employed to determine whether the effect of MK-212 on the repetitive extrasystole threshold is mediated by vagus nerves. In five dogs during 90 minutes of observation after the administration of MK-212, 0.1 mg/kg, the repetitive extrasystole threshold gradually increased by 12 ± 11%. This increase was not statistically significant. In the remaining seven dogs, given MK-212, 0.2 mg/kg, the threshold increased by 64 ± 30% (P < 0.05) from 21 ± 2 to 35 ± 6 ma after 90 minutes. The initial mean heart rate was 171 ± 8 and remained essentially constant.

Discussion

Verrier et al. (1974) stimulated baroreceptors in a vagotomized dog and demonstrated that a neural reflex inhibiting the outflow of sympathetic neural traffic to the heart markedly diminished the susceptibility of the nonischemic heart to ventricular fibrillation. Blatt et al. (1977) extended this observation to include the ischemic myocardium. An understanding of the sympatho-inhibitory neural apparatus is therefore relevant to the study of ventricular fibrillation and sudden cardiac death.

Franz et al. (1977) summarized anatomical and functional evidence that sympathetic preganglionic neurons are innervated by inhibitory bulbospinal serotonergic pathways originating in raphe nuclei of the brainstem. Experiments from diverse sources indicate that an increase in central nervous system serotonin inhibits sympathetic neural outflow from the brain. Baum and Shropshire (1975) recorded electrical activity directly from efferent cardiac, renal, and splanchnic sympathetic nerves of anesthetized cats. After the systemic administration of the serotonin precursor, 5-hydroxytryptophan, and the peripheral decarboxylase inhibitor, carbidopa, a dose-related reduction of as much as 87% of efferent sympathetic nerve traffic was recorded. The administration of serotonin or its precursor, 5-hydroxytryptophan, directly into the feline cerebral ventricles resulted in a similar reduction of sympathetic nerve traffic from the brain.
When the administration of serotonin precursors to dogs was accompanied by biochemical interventions designed to enhance the formation of serotonin in the brain, Antonaccio and Robson (1973, 1975) observed a reduction in blood pressure, left ventricular dp/dt, and severe depression of reflex pressor and cardiac accelerator responses to bilateral carotid artery occlusion. These cardiovascular alterations, which are consistent with decreased efferent central sympathetic tone, are inhibited by methysergide, a serotoninergic receptor antagonist (Antonaccio and Robson, 1975). Rabinowitz and Lown (1978) have demonstrated that neuropharmacological measures designed to elevate central nervous system serotonin reduced cardiac vulnerability to repetitive ventricular activity in the anesthetized dog, a result consistent with the hypothesis that elevated levels of central serotonin inhibit sympathetic neural outflow from the brain to the heart.

Anton-Tay et al. (1968) have shown that systemic administration of melatonin elevates serotonin levels in a region of the brain stem rich in cell bodies of serotoninergic nuclei (Fig. 6). The mechanism is as yet undefined. In the present study, administration of melatonin resulted in a significant increase in the stimulus current intensity required to evoke repetitive ventricular extrasystoles in both awake and anesthetized dogs. It is noteworthy that melatonin is an endogenous compound and that no enzyme inhibitors were required. The repetitive extrasystole method has been used extensively in our laboratory as an index of both susceptibility to arrhythmias and vulnerability to ventricular fibrillation (Rabinowitz et al., 1976; Matta et al., 1976). The repetitive extrasystole threshold maintains a constant relation to the ventricular fibrillation threshold both as to timing in the cardiac cycle and as to current requirement during a variety of autonomic neural interventions. This method obviates the profound neural as well as myocardial perturbations attending ventricular fibrillation and subsequent defibrillatory countershock. In addition, the repeated provocation of ventricular fibrillation is unsuitable on humane grounds for the study of central neural influences on cardiac arrhythmias in conscious animals.

The repetitive extrasystole threshold also increased after the intravenous administration of 5-methoxytryptophol, a compound occurring naturally in the pineal gland and closely related to melatonin, and 6-chloro-2-(1-piperazinyl)-pyrazine (MK-212), a synthetic agent chemically unrelated to melatonin or 5-methoxytryptophol but demonstrated to elicit distinct responses characteristic of serotonin receptor activation in the central nervous system (Clineschmidt et al., 1977). Melatonin, 5-methoxytryptophol, and MK-212 share a central serotoninergic action and each raises the repetitive extrasystole threshold.

Of these compounds, the most is known about melatonin to which a wide range of neural and endocrine effects have been ascribed (Wurtman and Moskowitz, 1977; Minneman and Wurtman, 1975, 1976). The primary source of melatonin in mammals is the pineal gland which is innervated by sympathetic neurons originating in the superior cervical ganglion (Wurtman and Moskowitz, 1977). When animals are kept in a dark environment, release of norepinephrine from sympathetic nerve terminals synapsing at the pineal gland stimulates melatonin synthesis and release. Circulating adrenomedullary catecholamines also facilitate melatonin release (Lynch et al., 1977). In an illuminated environment, retinal photoreceptors mediate inhibition of the pathway stimulating melatonin release (Wurtman and Moskowitz, 1977). Propranolol administration similarly attenuates the efflux of melatonin (Hansen et al., 1977).

There is meager information regarding the direct effect of melatonin on the heart. Barchas et al. (1967) noted that melatonin administered intravenously to dogs in a dose of 10 mg/kg altered neither cardiac contractility nor rhythm. The same dose of melatonin administered to cats did not change the blood pressure and did not affect the cardiovascular response to either adrenergic or cholinergic agents. Neither inotropic nor chronotropic characteristics of isolated guinea pig or rat heart were affected by melatonin. Mice receiving melatonin intraperitoneally (30 mg/kg) showed no alteration in gross behavior and no change in levels of norepinephrine in the heart or brain.

Clineschmidt et al. (1977) have shown that MK-212 produces a serotonin-like action in the central nervous system. When administered systemically to rats and mice, MK-212 elicited four distinct responses characteristic of serotonin-receptor activation in the brain. Administration of metergoline, a centrally acting serotonin antagonist, completely abolished all four of these effects of MK-212. The serotonin-mimetic actions were not altered after treatment with the peripherally acting serotonin antagonist, xylamidine. MK-212 inhibits neuronal...
uptake of serotonin in a dose-related fashion without altering uptake of norepinephrine or dopamine, but this action does not account fully for its serotonin-mimetic effect (Clineschmidt et al., 1978).

Several experiments were performed with metergoline to examine the hypothesis that enhancement of cardiac electrical stability by melatonin, methoxytryptophol, and MK-212 is mediated by a serotonergic mechanism. Metergoline is a specific serotonin antagonist, lacking activity at cholinergic, adrenergic, and histaminic receptor sites, and is effective in blocking central serotonin reflex responses to MK-212 in rodents (Clineschmidt et al., 1977). Metergoline alone had no significant effect on the repetitive extrasystole threshold or heart rate, but blocked responses to MK-212. This finding bolsters the supposition that a serotonergic mechanism mediates the effect of MK-212 on the threshold. The observation that metergoline alone did not alter the threshold suggests that in the control state there may be little tonic inhibition of sympathetic neural outflow by the serotonergic apparatus.

In summary, it has been found that the administration of either melatonin, 5-methoxytryptophol, or MK-212 raises the threshold of the vulnerable period for repetitive electrical activity in the canine ventricular myocardium. Since these agents share a central serotonergic action, and since the effect of MK-212 on the threshold is blocked by the specific serotonin antagonist, metergoline, one may surmise that a central serotonergic mechanism mediates the observed antiarrhythmic effect. MK-212 administration increased the repetitive extrasystole threshold despite bilateral vagotomy. The MK-212 action therefore does not depend on enhanced vagal outflow, although the increased dose requirement for MK-212 after vagotomy suggests that increased vagotonia may contribute in part to the effect of MK-212 on the heart rate and repetitive extrasystole threshold in the intact conscious animal. The findings are consistent with the hypothesis that the central serotonergic apparatus influences cardiac rhythm by inhibiting sympathetic outflow, but no new confirmatory evidence has been adduced.

Gillis and coworkers (Gillis et al., 1976; Helke et al., 1976, 1978) have presented findings suggesting that a reduction in central serotonergic activity, rather than an increase, mediates a sympatho-inhibitory antiarrhythmic effect. Electrical stimulation of the dorsal raphe serotonergic nuclei in anesthetized cats provoked ventricular arrhythmia. This effect was prevented by propranolol (Gillis et al., 1976). Ventricular tachycardia that appeared in anesthetized cats and dogs during digitalis intoxication reverted to sinus rhythm after methysergide was infused (Helke et al., 1976, 1978). The apparent contradiction between these studies and our own is typical of the conflicting and controversial results that have been obtained regarding cardiovascular effects of central serotonergic mechanisms. Chalmers and Wing (1975) and Smits and Struyker-Boudier (1976) point out that such differences may be due to differences in species, use of anesthetics, nonspecificity of chemicals employed, variation in serotonin effect at various levels of the nervous system, and differences in the end points observed in various experimental models. It might be noted also that serotonin concentrations do not necessarily reflect serotonin turnover rates or serotonergic neuronal activity. Finally, there may be more than one type of serotonin receptor in the brain (Bourgoign et al., 1978). At this early stage of investigation, we are more impressed by the confirmation that serotonergic neurons are intimately involved in the regulation of arrhythmogenic sympathetic nerve traffic than by divergences in early results.

These findings have profound clinical implications. Evidence that is now being adduced indicates that manipulation of dietary amino acids affects the chemistry of serotonin in the brain (Fernstrom and Wurtman, 1971; Wurtman and Fernstrom, 1976). Nutritional approaches may therefore provide an interesting avenue for manipulating sympathetic neural tone to the heart. Noteworthy, too, is the clinical observation that sleep is associated with a reduction in grade and frequency of ventricular arrhythmia (Lown et al., 1973). Are these sleep-induced alterations a consequence of the diurnal increase in melatonin elaboration? Also relevant is the ubiquity of arrhythmias in intensive care units where patients are exposed to continuous light. Most important is the fact that modern neuropharmacology is making available agents which permit precise alterations in brain neurochemistry and thereby may permit elicitation of discrete cardiovascular effects.

Acknowledgments

We gratefully acknowledge the design and construction of electronic equipment by Nicholas Jordan, the technical assistance of Joseph Melman, Ph.D., of George LeBrun, Edward Burke, and Sally Carr, and the secretarial assistance of Claudia Kenney and Mildred Dewire. We also acknowledge the providing of cardiac pacing catheters by Lawrence W. Shearson (Medtronic), of MK-212 by Dr. Bradley V. Clineschmidt (Merck), and of metergoline by Dr. Claudio Praga (Farmitalia).

References

Baum T, Shropshire AT: Inhibition of efferent sympathetic nerve activity by 5-hydroxytryptophan and centrally administered 5-hydroxytryptamine. Neuropharmacology 14: 227-233, 1975
Beattie J, Brow GR, Long CNH: Physiological and anatomical evidence for the existence of nerve tracts connecting the
Blatt CM, Verrier RL, Lown B: Acute blood pressure elevation and ventricular fibrillation threshold during coronary artery occlusion and reperfusion in the dog. Am J Cardiol 39: 523-528, 1977
Dikshit BB: Production of cardiac irregularities by excitation of the hypothalamic centers. J Physiol (Lond) 81: 382-394, 1934
Fernstrom JD, Wurtman RJ: Brain serotonin content: physiological dependence on plasma tryptophan levels. Science 173: 149-152, 1971
Garrey WE: Some effects of cardiac nerves upon ventricular fibrillation. Am J Physiol 21: 283-300, 1908
Hunt R: Direct and reflex acceleration of the mammalian heart with some observations on the relations of the inhibitory and accelerator nerves. Am J Physiol 2: 395-470, 1899
Levy AG: The exciting causes of ventricular fibrillation in animals under chloroform anesthesia. Heart 4: 319-378, 1913
Lynch HJ, Ho M, Wurtman RJ: The adenal medulla may mediate the increase in pineal melatonin synthesis induced by stress, but not that caused by exposure to darkness. J Neural Transm 40: 87-99, 1977
Rabinowitz SH, Lown B: Central neurochemical factors related to serotonin metabolism and cardiac ventricular vulnerability for repetitive electrical activity. Am J Cardiol 41: 516-522, 1978
Central serotonergic agents raise the repetitive extrasystole threshold of the vulnerable period of the canine ventricular myocardium.

C M Blatt, S H Rabinowitz and B Lown

Circ Res. 1979;44:723-730
doi: 10.1161/01.RES.44.5.723

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/44/5/723