The latest knowledge regarding central nervous system control of cardiac function has been summarized by Weinberg. The importance of centrally mediated effects has not been appreciated and emphasis has been placed on the myocardium. The effects of cardiac glycosides, quinidine and procaine amide on the heart are well known, but evidence suggests that one of the principal sites of action of the glycosides may be elsewhere than on the myocardium itself. This may also be true for the other drugs. It is not possible to derive satisfactory conclusions concerning centrally mediated effects by the experimental use of muscle strips, isolated organs or anesthetized animals because of the absence of, or the suppression of the central nervous system. However, it may be possible to separate the central and peripheral effects by the introduction of drugs into the third ventricle of trained unanesthetized dogs.

METHODS

Twenty-five normal mongrel dogs of both sexes weighing 7.8 to 19.5 kg. were anesthetized with sodium pentobarbital, 35 mg/kg., intravenously. An indwelling metal cannula was inserted through a trephine hole and attached to the skull. The cannula extended into the third ventricle and it was possible to obtain a sample of cerebro-spinal fluid upon aspiration. Each dog received 600,000 U of repository penicillin intramuscularly and the animals were used a week later in the unanesthetized state. All third ventricle injections were made via a polyethylene tube attached to the cannula. The total volume injected per dose was 0.5 ml. except in the case of the 100 mg. dose of procaine amide where the volume was 1.0 ml. The intraventricular drug doses were: strophanthin-K, 0.02 to 0.55 mg.; quinidine sulfate, 5 to 50 mg.; and procaine amide, 50 to 100 mg. Intravenous injections were made via the anterior subcutaneous vein of the foreleg using the doses stated in the text. The electrocardiograms were obtained with a Sanborn Viso-Cardiette using Lead II. Table 1 gives typical results obtained by the different routes of administration with all of the drugs, indicating the time intervals for the appearance of the various effects.

RESULTS

Effects of Strophanthin-K and Quinidine Alone

The intraventricular injection of 0.02 mg. of strophanthin-K in an animal produced characteristic extrasystoles followed by paroxysmal ventricular tachycardia, whereas intravenous administration of 1.5 mg. eight days later produced no such electrocardiographic changes. The electrocardiographic changes after third ventricle injection were not related to the solvents used because they were not observed after intraventricular injection of 0.5 ml. of 0.9 per cent normal saline or propylene glycol.

Third ventricle injection of 10 mg. of quinidine sulfate produced paroxysmal ventricular tachycardia, rate 260, with alternation, fol-
### Table 1.—Effects of Cardio-Tonic Drugs in Unanesthetized Dogs

<table>
<thead>
<tr>
<th>Animal, Sex and Weight</th>
<th>Drug and Route of Administration</th>
<th>Time Min.</th>
<th>Pulse Rate</th>
<th>Cardiac Effects</th>
<th>Secondary Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 8 Male 19.5 kg.</td>
<td>Quinidine sulfate 50 mg. V.C.</td>
<td>0</td>
<td>80</td>
<td>Alternating nodal extrasystoles</td>
<td>In 2 min., mydriasis, urination, defecation, mucous membrane pallor, complete anesthesia, but corneal reflexes present.</td>
</tr>
<tr>
<td></td>
<td>Strophanthin-K 0.5 mg. V.C.</td>
<td>30</td>
<td>150</td>
<td>Sinus tachycardia</td>
<td>Salivation, mucous membrane pallor, persistent anesthesia, death by respiratory failure.</td>
</tr>
<tr>
<td>No. 2 Male 16 kg.</td>
<td>Strophanthin-K 0.55 mg. V.C.</td>
<td>0</td>
<td>70</td>
<td></td>
<td>Emesis, lateral and vertical nystagmus, mydriasis.</td>
</tr>
<tr>
<td></td>
<td>Quinidine sulfate 9 mg. V.C.</td>
<td>12</td>
<td>320</td>
<td>In 4 min. ventricular extrasystoles then paroxysmal ventricular tachycardia</td>
<td>Anesthesia.</td>
</tr>
<tr>
<td></td>
<td>Pentobarbital Na 120 mg. I.V.</td>
<td>23</td>
<td>150</td>
<td>Sinus tachycardia</td>
<td>Mydriasis, orbicular muscle twitching, tachypnea, opisthotonus, abdomen tense.</td>
</tr>
<tr>
<td>No. 22 Male 12 kg.</td>
<td>Strophanthin-K 0.5 mg. V.C.</td>
<td>0</td>
<td>55</td>
<td>Periodic P wave suppression, couples beats</td>
<td>Tense, but quiet.</td>
</tr>
<tr>
<td></td>
<td>Quinidine sulfate 800 mg. I.V. in five minutes</td>
<td>9-14</td>
<td>240</td>
<td>Paroxysmal bifocal ventricular tachycardia</td>
<td>One brief convolution. Anesthesia, expired in 12 hours.</td>
</tr>
<tr>
<td></td>
<td>Pentobarbital Na 120 mg. I.V.</td>
<td>15</td>
<td>140</td>
<td>Sinus tachycardia</td>
<td>Respiratory failure.</td>
</tr>
<tr>
<td>No. 20 Female 13 kg.</td>
<td>Strophanthin-K 0.5 mg. V.C.</td>
<td>0</td>
<td>100</td>
<td>Normal</td>
<td>In 3 min.: mydriasis, blanching of mucous membrane, salivation, barking, tachypnea. Muscle tension, excited. Convulsive jerking.</td>
</tr>
<tr>
<td></td>
<td>Quinidine sulfate 800 mg. I.V. in five minutes</td>
<td>6</td>
<td>200</td>
<td>Auricular tachycardia</td>
<td>Respiratory failure.</td>
</tr>
<tr>
<td>No. 18 Female 14.2 kg.</td>
<td>Procaine amide 100 mg. V.C.</td>
<td>0</td>
<td>75</td>
<td>Alternating ventricular extrasystoles</td>
<td>Lateral nystagmus, salivation, mydriasis.</td>
</tr>
<tr>
<td></td>
<td>Strophanthin-K 0.5 mg. V.C.</td>
<td>30</td>
<td>90</td>
<td>Alternating ventricular extrasystoles</td>
<td>Slow respiration.</td>
</tr>
<tr>
<td></td>
<td>Hexamethonium 120 mg. I.V. 80 mg. I.V.</td>
<td>30</td>
<td>280</td>
<td>Alternating ventricular extrasystoles</td>
<td>Slow respiration, pupils constricted. Complete relaxation, no salivation. Respiratory failure.</td>
</tr>
</tbody>
</table>

**V.C. = Third ventricle injection. I.V. = Intravenous injection**

**Cardiac Effects**:
- Alternating nodal extrasystoles
- Sinus tachycardia
- Ventricular tachycardia
- Sinus tachycardia
- A-V dissociation

lowed by a diminishing sinus tachycardia. Immediate secondary effects included retching, defecation, urination, nystagmus, respiratory depression and almost complete general anesthesia. Complete recovery followed and the animal showed no after effects. Fig. 1 gives typical electrocardiograms obtained with both drugs.

Quinidine-Strophanthin-K Antagonism

Intraventricular injection of quinidine sulfate in doses ranging from 5 to 50 mg. in five experiments produced paroxysmal auricular tachycardia with rates varying from 205 to 280. Subsequent intraventricular injection of either 0.25 or 0.5 mg. of strophanthin-K failed to induce the characteristic strophanthin-K arrhythmia. However, in all cases, the secondary effects were quite marked. One animal given 50 mg. of quinidine sulfate intraventricularly developed a paroxysmal ventricular tachycardia, rate 380, with transitory alternating upper nodal extrasystoles followed by a declining rate. The usual symptoms of toxicity were observed with the addition of mydriasis, buccal mucous membrane blanching and general anesthesia approximating Stage III, Plane II with corneal reflexes still present. Intraventricular injection of 0.5 mg. of strophanthin-K resulted in the characteristic ventricular tachycardia, rate 230, but the duration was only two minutes. Thereafter, the pulse slowed to 140 with regular sinus rhythm. However, a complete A-V block ensued and the animal expired from respiratory failure. This series of experiments demonstrated the suppression of the characteristic strophanthin-K electrocardiographic pattern by prior administration of quinidine sulfate. Fig. 2 gives a typical record.

In five control experiments in which quinidine sulfate, 10 to 100 mg., and strophanthin-K, 0.5 mg., were given intravenously, no toxic symptoms or abnormal changes in the electrocardiogram were observed. However, a transient bradycardia was observed with 1 mg. of strophanthin-K.

In two experiments an attempt was made to stop the centrally induced strophanthin-K effect with intravenous quinidine sulfate. The characteristic strophanthin-K arrhythmia was only slightly modified by two 250 mg. doses of quinidine sulfate and ventricular fibrillation and respiratory paralysis occurred quickly. When 800 mg. of quinidine sulfate was given in five equal doses, over a longer time interval, the paroxysmal ventricular tachycardia reverted to a sequence of regularly alternating unifocal ventricular extrasystoles, sinus tachy-
Cardia, rapid nodal tachycardia, alternating flutter, fibrillation and finally a rapid sinus rhythm. A reduction in rate was finally brought about by the injection of 120 mg. of pentobarbital. Respiratory failure was not observed probably because of the slower rate of administration of the quinidine sulfate.

**Procaine Amide-Strophanthin-K Antagonism**

Three experiments were performed in which procaine amide in doses of 50, 100 and 100 mg., respectively, were injected intraventricularly, followed one-half hour later by either 0.05 or 0.5 mg. of strophanthin-K. In each experiment the characteristic strophanthin-K paroxysmal ventricular tachycardia was prevented by prior administration of procaine amide. However, in one experiment a modified strophanthin effect consisting of irregularly occurring sinus pauses, then sinus tachycardia, followed by alternating ventricular extrasystoles was seen. These were stopped immediately by 60 mg. of pentobarbital intravenously. The generalized side-effects of intraventricular procaine amide were limited to nystagmus, defecation, slight twitching of the facial musculature and Stage III plane II anesthesia. Furthermore, the procaine amide reduced the side-effects usually observed after strophanthin-K administration. The marked apprehension, convulsions, and exophthalmus did not occur and the muscular tremor was minimal. However, mydriasis, moderate nystagmus, salivations and tonic dorsal spasm of the neck musculature were seen. Where only 0.05 mg. of strophanthin-K was given death was delayed eighteen hours. Respiratory failure occurred sooner with the 0.5 mg. dose. Fig. 3 gives a typical electrocardiogram.

When the characteristic arrhythmia was induced by intraventricular administration of 0.4 mg. of strophanthin-K, the intraventricular injection of 100 mg. of procaine amide 30 minutes later quieted the animal, but death occurred in six hours. The usual strophanthin side-effects were not greatly modified.

In a control experiment in which 100 mg. of procaine was given intravenously, there were no electrocardiographic changes or secondary effects on the animal.

In two experiments an attempt was made to stop the centrally induced strophanthin-K effect with intravenous procaine amide, 75 mg/kg. Intraventricular injection of 0.05 mg. of strophanthin-K produced, within 5 minutes, SA node depression with the pulse rate dropping from 100 to 60, together with bigeminal normal beats. The Q-T interval was not altered, but T wave reversal occurred. Mydriasis, defecation and salivation were observed. No further electrocardiographic changes occurred during the next one-half hour so the animal was given 0.175 mg. of strophanthin-K, whereupon the rhythm became one of alternating ventricular extrasystoles, rate 108. After intravenous procaine amide, a sinus rhythm, rate 160, appeared within 6 minutes of the completion of the injection. The animal, previously in tremor with profuse salivation and lateral nystagmus, became quiet although he continued to have the tremor, salivation, mydriasis and mucous membrane pallor. The
side-effects ceased after intravenous injection of 120 mg. of pentobarbital, but the sinus tachycardia persisted. Similar results were obtained with the second animal although the heart rate reached a higher level. In both cases, death was due to respiratory failure.

Hexamethonium-Strophanthin-K Antagonism

If the cardiac abnormalities observed after third ventricle injection of strophanthin-K were centrally induced, it should be possible to return the heart to a normal rhythm by interrupting the autonomic pathways involved. Under the conditions of our experiments, it appeared that this could best be accomplished by the intravenous administration of a ganglionic blocking agent. In two dogs, normal rhythm was reestablished by the intravenous administration of approximately 15 to 20 mg/kg of hexamethonium chloride while in a third animal 37.3 mg/kg was required, see Figure 4 for a typical record. The results indicate that hexamethonium interrupted the flow of impulses to the myocardium set in motion by the intraventricular injection of strophanthin-K. Paton and Zaimis have pointed out that the ganglionic blockade produced by hexamethonium in the unanesthetized dog will abolish cardiac arrhythmias, but a tachycardia similar to that seen after sympathectomy will be present. We also observed a tachycardia in our unanesthetized dogs. However, there was a gradual reduction in this chronotropic effect and a return to a rate comparable to the pretreatment control value prior to death. Whether or not hypoxia played a part in this latter effect cannot be determined with the information presently available. On the other hand, it is unlikely that the return to normal rhythm could be attributed to a central action of hexamethonium because Paton and Zaimis have reported that this drug has a very slow entry into the cerebro-spinal fluid whereas its peripheral ganglionic blocking effect occurs extremely rapidly. Furthermore, hexamethonium must have blocked transmission of impulses through the superior cervical ganglia and the submaxillary ganglia because the mydriasis and salivation observed immediately following the intraventricular injection of strophanthin-K disappeared. Paton and Zaimis have shown that these ganglia are among the most easily blocked of all those affected by hexamethonium.

![Figure 3](image3.png)

**Figure 3.** Effect of Strophanthin After Procaine Amide. Procaine Amide, 100 mg. intraventricularly after control record, followed by strophanthin-K, 0.5 mg., 30 minutes later. Time sequence of records was 0, 5, 15, 30, 40 and 60 minutes respectively.

![Figure 4](image4.png)

**Figure 4.** Effect of Hexamethonium on Strophanthin Arrhythmia. Control record followed by 0.5 mg. of strophanthin-K intraventricularly, then 20 mg/kg of hexamethonium chloride intravenously 7 minutes later. Time sequence of records was 0, 3, 11 and 19 minutes respectively.
DISCUSSION

The proof that the cardiac irregularities, observed after third ventricle injection of strophanthin-K, are centrally mediated is fourfold: 1) The rapidity of onset, two to three minutes, would hardly allow enough time for diffusion of sufficient concentration of the drug from the cerebrospinal fluid into the systemic circulation. 2) Intravenous injection of the same size total dose, 0.25 to 0.5 mg., produced no alteration in cardiac rhythm whereas a dose of 1.0 mg. produced a transient bradycardia instead of a paroxysmal ventricular tachycardia. 3) Intraventricular administration of either quinidine sulfate or procaine amide prior to strophanthin-K modified or blocked the usual cardiac effects of the latter. 4) Intravenous hexamethonium produced a reversion to normal rhythm by blocking sympathetic transmission at the ganglia. Furthermore, as Korth et al had shown earlier, barbiturate anesthesia abolished the strophanthin-K induced cardiac irregularity.

Cardiac irregularities observed clinically have many causes, one of which is related to the use of cardiac glycosides and it has been pointed out by Gold and Zapata-Diaz et al that the use of quinidine in such cases was of questionable value and could be dangerous. Our results with intravenous quinidine would support their contention concerning the questionable value of this drug in such instances.

Fox et al observed a ventricular tachycardia and ventricular fibrillation following intravenous procaine amide in a patient with Wolff-Parkinson-White syndrome. Their records closely resemble ours and indicate that caution should be exercised in the employment of procaine amide in cardiac conditions, particularly those in which cardiac glycosides have been used.

The type of electrocardiographic changes seen after intraventricular strophanthin-K or procaine amide, irregularly occurring sinus pauses, appear to be similar to those included in de Boer's grouping of the Luciani pauses and similar to those periods known to occur in digitalis toxicity.

SUMMARY

Injection of strophanthin-K into the third cerebral ventricle of trained unanesthetized dogs produced cardiac irregularities including bigeminy, trigeminy, bradycardia, tachycardia, ventricular extrasystoles and paroxysmal ventricular tachycardia. Intravenous injection of equal or larger doses of this drug in the same or other dogs had little or no effect on the electrocardiogram.

Injection of quinidine sulfate into the third cerebral ventricle of trained unanesthetized dogs produced paroxysmal auricular tachycardia, nodal and ventricular extrasystoles and paroxysmal ventricular tachycardia. Under the same conditions, the intravenous injection of equal or larger doses of the drug caused little or no electrocardiographic changes.

The arrhythmic effect from intraventricular injection of strophanthin-K was prevented or modified by prior intraventricular injection of either quinidine sulfate or procaine amide.

Intraventricular injection of either quinidine sulfate or procaine amide produced Stage III Plane II anesthesia.

The arrhythmic effects of intraventricular strophanthin-K may be terminated or modified by intravenous quinidine sulfate, procaine amide or sodium pentobarbital. They can be entirely blocked by intravenous hexamethonium chloride.

The centrally induced cardiac effects of strophanthin-K and quinidine sulfate are accompanied by autonomic manifestations resembling those seen in cases of clinical digitalis and quinidine toxicity.

ACKNOWLEDGMENT

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REFERENCES

Influence of Stimulating the Cervical Sympathetics on Blood Flow of the Cerebral Gray and White Matter in Dogs

The Gibbs' technic for recording changes in rate of cerebral blood flow has recently been improved. Highly sensitive resistance thermometers were substituted for thermal junctions, the advantage of the former being that the sounds inserted into tissues need not be heated to more than 0.5° to 2° C above tissue temperatures. The differential method of recording was replaced by one that compared a standard temperature with that of the heated sound.

By inserting such recording elements into various regions of the cerebrum of anesthetized dogs it was found that stimulation of the cervical sympathetic reduced blood flow in reproducible fashion in the white substances but only occasionally in the gray matter of the cortex or basal ganglia. This does not preclude innervations by other pathways. Section of the cervical sympathetic nerves failed to influence cerebral blood flow.

The threshold of stimulation required to produce these effects was raised, or stimulation failed, when the blood CO₂ content was either increased or decreased away from a critical value. It is estimated that, at normal ranges of CO₂, nerve impulses would have little or no effect on cerebral blood flow; but they could be operative under pathologic conditions.

The authors stress the existence of two systems of responsiveness, a rapid and a slow; the former was always reversible, the latter, infrequently. In our opinion, the possibility that technical rather than physiologic differences were concerned in the case of "slow responses" should be considered more carefully.

For details see N. Ludwig and M. Schneider- Arch. f. d. ges. Physiol. 259, 43, 1954.
Centrally Mediated Effects of Cardiac Drugs: Strophanthin-K, Quinidine and Procaine Amide
S. J. WEINBERG and THOMAS J. HALEY

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