CONCERNING THE MECHANISM PRODUCING AN ADRENALIN MYOCARDITIS

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Spinal shock expresses itself, as is well known, by severe reflex suppression mainly below the level of sectioning of the spinal cord. This permits the use of spinal section as a method for the temporary exclusion of nerve centers in the distal portion.

Our previous studies [1] have shown that in rats whose spinal cord had been severed at the $C_8 - T_1$ level and who had thus had induced in them spinal shock, injections of adrenalin during this period of shock will either not induce the development of myocarditis at all or, at most, induce it in only a light form. This permits the supposition that the inflammatory myocardial process is suppressed in these experiments because the spinal centers of cardiac innervation (T_1–T_5) are in the shock zone and, therefore, the reflexes associated with them are greatly hampered. Such a supposition is supported by the results of experiments with sectioning of the spinal cord at the lumbar level and with experiments in which decortication is performed; severing the lumbar cord does not prevent adrenalin myocarditis; decortication, which intensifies reflex activity, also makes the adrenalin myocarditis develop most severely. It still did not clarify the cardiac alterations accompanying these three indicated operations and did not reveal the relations between these changes and the development of adrenalin myocarditis.

The present study was undertaken in an effort to answer these questions, and we have repeated our previous studies, with some additional work and use of the ECG machine.

EXPERIMENTAL METHODS

The spinal cord was severed at the $C_8 - T_1$ level in 27 rats. ECG's (the three standard and fourth chest leads) were taken before the operation and 24 and 48 hours after the operation. Then, the "myocarditis" dose of adrenalin (0.5 cc) was given intramuscularly and the ECG was repeated (40 minutes and 24 hours after the injection).

EXPERIMENTAL RESULTS

Of the 27 rats operated, 2 died within two days of the operation, 11 perished shortly after the adrenalin injection, and the remaining 14 were sacrificed 24 hours after the injection of adrenalin. The rat hearts were studied microscopically (frozen sections stained with Sudan III and hematoxylin). In 7 rats no signs of myocarditis could be found, in 6 rats the myocarditis appeared to be quite mild, and only in one rat was it marked. In the control material, the same dose of adrenalin given to 52 healthy rats induced myocarditis in 46 rats.

In our previous experiments (21 operated rats) myocarditis did not develop in 12 rats, and was only

mildly evident in 9. In the control experiments myocarditis developed as a rule (39 out of 43 rats receiving 0.5 cc adrenalin and 151 out of 153 receiving 0.8 cc).

This demonstrates that in two groups of experiments with sectioning of the spinal cord at level $C_8 - T_1$ the response with a development of a myocarditis to an injection of adrenalin was almost eliminated.

ECG's taken 24 and 48 hours after the operation (before injecting the adrenalin) showed considerable abnormalities. All rats had bradycardia of varying degree, and some had arrhythmias.

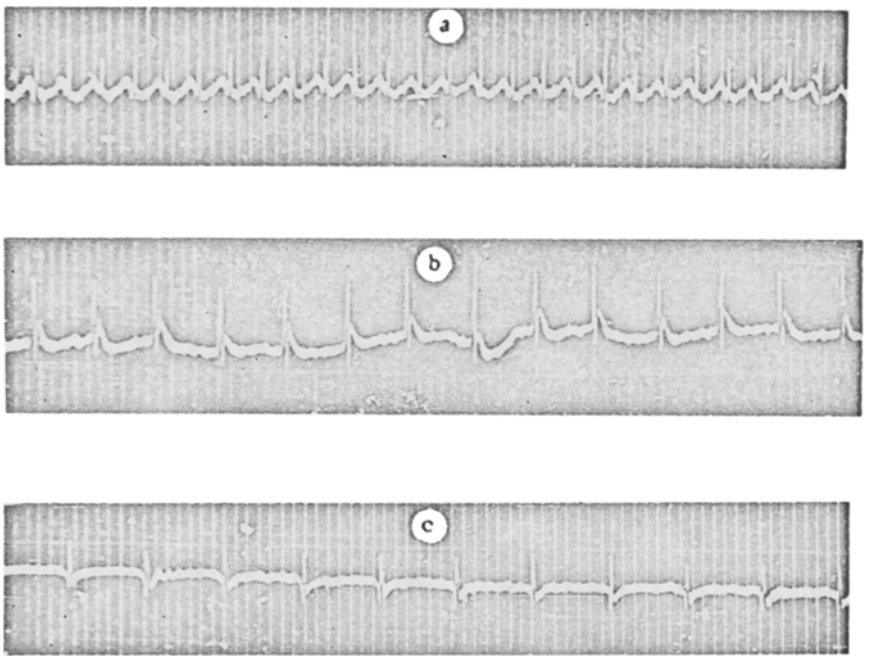
The normal rat heart rate is 480-500 beats per minute. In rats the spinal cord of which had been severed at the C_8–T_1 level the pulse varied from 160 to 400 beats per minute.

The ECG changes indicated severe metabolic disturbances and conduction myocardial disturbances (lowering or elevation of R wave, S–T interval shifts in the chest and, sometimes, in the standard leads, fragmentation of the QRS complex in the chest lead, biphasic or inverted T).

It should be noted that after the indicated operation the ECG waves in the rats altered much as after injections of large doses of adrenalin.

On the ECG taken 40 minutes after the adrenalin injection, there could be noted an acceleration of the pulse by 20-60 beats per minute while in the others there could be observed an aggravation of those changes noted after the operation. Twenty four hours after the injection the pulse either returned to normal post-operative levels or else the bradycardia became more pronounced. In rats with a developing myocarditis the ECG would reveal appearance or deeper inversions of the T wave. Rats not developing a myocarditis showed no further ECG alterations (Figure).

The appearance of the bradycardia after the spinal cord sectioning above the level of cardiac innervation is evidence in our experiments of the depressed state of the sympathetic centers in this zone.



Experiment with introduction of adrenalin after operation severing the spinal cord at level $C_8 - T_1$, rat No. 1062 (ECG taken in chest lead IV).
a) ECG before operation. Pulse is 480 per minute. R is 0.5 mv; b) ECG 24 hours after the operation. Pulse is 260 per minute. S-T interval shift. R is 1.1 mv. T is inverted; c) ECG 24 hours after injecting 0.5 cc adrenalin. Pulse is 170 per minute. T is isoelectric. No myocarditis was seen histologically.

It is well known that injuries precisely in the cervical spinal cord region can give a bradycardia down to 40 systoles per minute [3, 4].

The variations in the bradycardia observed by us may be due to variations in the depth of shock as well as due to variations in the locations of the cardiac sympathetic centers.

In order to observe further cardiac state and activity after section of the spinal cord at level of C_8-T_1, 30 rats were kept as long as possible after the surgery. The rats were catheterized every 6-8 hours, a hematuria being observed early. In most of the rats (26) the bradycardia became more marked and the ECG changes observed early became more marked and could be seen in all four leads. The rats died within 1 to 9 days after surgery.

Histologic examination of the rat hearts shows that even within the first day after operation the myocardium reveals a marked hyperemia (neuroparalytic ?) and marked cloudy swelling of the muscular fibers. In cases of death in later stages the myocardium showed extravasations and increasing albuminous dystrophy.

It must be assumed that the muscular changes seen in the myocardium are only a partial expression of the profound metabolic alterations which are reflected in the ECG within the first day of the operation. It is most unlikely that the adrenalin-sensitive biochemical systems within the muscle cells and the myocardial receptors remain intact functionally with such myocardial alterations. For this reason it is difficult to determine where the reflex arc was severed and so enabled the adrenalin not to have the usual myocarditis effect. This is especially difficult in the short experiments where the cessation of the existence of central impulses cannot be differentiated from the spinal section itself affecting the spinal cardiac centers.

In our previous experiments [2] we established that introduction of sympatholin (adrenalin antagonist) as late as 5-8 minutes before the adrenalin injection prevents the possibility of an adrenalin myocarditis developing. It should be noted that intramuscular injection of the sympatholin is accompanied by bradycardia. In some of the rats this bradycardia could be observed within 5 minutes of the injection (2 rats), while within 1 hour the bradycardia was present in all 9 rats.

It is possible that a part of the antagonistic action on the heart by the sympatholin is due to inhibition of the sympathetic centers of cardiac innervation.

The data presented above and the conclusions drawn from it seem more convincing when juxtaposed with the results seen after the spinal cord had been transected at the lumbar level. When this is done, the spinal cardiac sympathetic centers remain outside the zone of spinal shock. The spinal cord was transected at the lumbar level in 14 rats. Adrenalin was injected 48 hours later and the rats were sacrificed 24 hours after the adrenalin injection.

Histological examination proved that all these rats had adrenalin myocarditis, in varying degrees of severity just as is seen in the usual control material (unoperated rats after adrenalin injections).

After such an operation cardiac rhythm and ECG remain unchanged. After the adrenalin is introduced the ECG reflects the changes characteristic of the oncoming myocarditis (voltage changes in the waves, alterations in S-T interval and inversions of the T wave).

These results demonstrate the decisive role played by the level at which the spinal section is performed and the significance of the spinal shock in causing cardiac alterations and the appearance of adrenalin myocarditis.

With the goal of increasing the reflex sensitivity of the spinal centers, 20 rats were decorticated-partial removal of the cerebral cortex from the cerebral hemispheres. In some of these rats immediately after the surgery epileptiform convulsive seizures were observed. All the rats during the entire post-operative period had marked motor stimulation.

Adrenalin (0.5 cc) was introduced on the 9th post-operative day and the rats were sacrificed 24 hours after the injection. Adrenalin myocarditis was present in 18 rats, in the majority of them, very marked. Repeated ECG's done after the operation showed that pulse fluctuations in the operated rats were minimal and the ECG changes were different from those seen after spinal cord transections. Basically, the wave voltages became somewhat altered, sometimes a deep S wave being seen. The S-T interval and the T wave seemed stable, which leads us to suppose that decortication did not carry in its train profound metabolic alterations in the myocardium.

Putting together the results of this experiment with the experiments in which the spinal co. ...as transected at the cervical and lumbar levels, we believe that the whole complex of alterations evoked by decortication permitted an intensification of the adrenalin myocarditis by reason of a release of cortical inhibition of the reflex sensitivity of the spinal cord, in part, of course, including the cardiac centers.

Also, it may be that the absence of any basic upset in myocardial metabolism after cerebral decortication (as far as can be judged by the ECG) is another pre-condition for the myocarditis developing after the adrenalin injection.

The data obtained need further physiological and pharmacological analysis. In part it is important to study how spinal shock affects the action of other substances capable of producing myocarditis.

However, a summary of the work already done permits some conclusions.

When the spinal cord is transected above the zone of the cardiac spinal centers (at level C_8–T_1), the rats develop bradycardia and ECG changes testifying to changes in contractility and the metabolic myocardial processes. Histologic studies of such rat hearts revealed myocardial hyperemia and albuminous dystrophy of the muscle fibers.

Introduction of adrenalin into the operated rats does not cause further qualitative ECG changes and an adrenalin myocarditis either does not develop at all or is minimal. This is associated with the functional upset of the cardiac sympathetic innervation, the spinal cardiac centers being within the zone of shock.

When lumbar level spinal cord transection is done, the cardiac sympathetic centers are above the shock level. The cardiac rhythm and ECG remain unaffected. Introduction of the same doses of adrenalin produces in the operated rats an adrenalin myocarditis which gives the characteristic ECG changes.

The extent of the adrenalin myocarditis is variable and comparable to that seen in the controls.

After decortication cardiac rhythm likewise is undisturbed and the ECG changes are inconstant and have a different character from that seen after transection of the spinal cord at the C_8–T_1 level.

It must be assumed that cardiac contractility and myocardial metabolic processes are basically unaffected by such an operation.

Adrenalin introduced after such surgery causes an especially intense development of a myocarditis. This may be due to the heightened irritability of the subcortical centers and the spinal cord in these decorticated animals.

The experiments presented above seem to confirm the fundamental role played by the nervous system in the development of an adrenalin myocarditis. In part, the state of functional condition of the spinal cord cardiac centers seems to be important. From this it seems logical to conclude that the variations seen in the adrenalin myocarditis produced in rats after a single injection of adrenalin must be associated with individual variations in the reflex reactions of the animals.

SUMMARY

Adrenalin myocarditis was studied in rats. The effects of spinal cord transections above and below the spinal cord cardiac centers were studied. Transection at C_8–T_1 level produced spinal cord shock below that level, knocking out the cardiac sympathetic centers. Adrenalin myocarditis in this group of rats was either very mild or absent.

Transection below the centers (at lumbar level) did not give results differing materially from the group in which the myocarditis was induced by the usual single adrenalin injection. This seems to be because the spinal cord cardiac sympathetic centers remained unaffected by the transection.

Finally, decortication seemed to intensify the adrenalin myocarditis; probably because of the release of the central inhibition of the spinal cardiac sympathetic centers.

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