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ON THE PHYSIOLOGICAL ACTION OF ULEXIN.

By J. ROSE BRADFORD, B.Sc., M.R.C.S.

(*From the Physiological Laboratory of University College, London.*)

ULEXIN is an alkaloid that has recently been prepared by Mr Gerrard[1] (Pharmacist to University College Hospital) from the seeds of the common gorse, Ulex Europaeus, and I have to thank him for the material used in this investigation. The hydrobromate was the salt used since this salt crystallizes more readily than any other, and so the drug is obtained in a greater degree of purity. My best thanks are due to Dr Ringer, F.R.S., (at whose suggestion the work was begun), not only for the very kind manner in which he has assisted me with his advice, but also for the many occasions on which he was present at the experiments, and for the assistance I derived from his valuable criticism.

Ulexin is an alkaloid that has a very general action on the tissues, besides a highly specialized action on the respiration, and so experiments were first made on frogs, mainly with regard to its action on muscle and nerve; and subsequently on the cat and dog. A few observations were also made on the eel with regard to the action of the drug on the heart, since in this animal the phenomena of inhibition[2] are so much more readily investigated than in the frog. Since the work was begun, a paper by a French observer[3] has appeared, detailing a few experiments on the frog only. Although the results obtained by myself agree in the main with his, yet there are some slight differences, and hence it may be more convenient if my own observations are given first, and the points of difference mentioned later.

[1] A. W. Gerrard. *Pharmaceutical Journal.* Aug. 7, 1886..

[2] J. A. McWilliam. *Journal of Physiology.* Vol. VI. Page 192.

[3] Pinet. *Archives de Physiologie.* Feb. 1887. Page 89.

1. Action of Ulexin Hydrobromate on the Frog.

The injection of 5 mgrms. of Ulexin hydrobromate into the dorsal lymph space of a frog, weighing 30 grms, is followed in about five minutes by cessation of the respiratory movements, abolition of reflexes and complete paralysis of all voluntary movement; the circulation however is still carried on. The muscles are found to respond to direct electrical excitation, but not to nerve excitation; the strongest currents, when applied to the sciatic nerve, failing to produce any contraction of the leg muscles. On opening the pleuroperitoneal cavity, it is seen that the heart is slowed and weakened, and does not contract completely, and hence does not become completely emptied of blood during the systole. Stimulation of the vagus does not inhibit it, although the application of the electrodes to the sinus does. From this experiment, it is seen that Ulexin acts as a nerve poison, and, from the following one, it is found that the peripheral structures, presumably the end plates, are the structures that are poisoned. In a frog weighing 32 grms. the brain was destroyed, and the sciatic nerve dissected out on one side; a strong ligature was then tightly tied round the remaining tissues of this leg, and 10 mgrms of Ulexin injected under the skin of the back. In about a quarter of an hour, the unprotected parts were quite paralyzed, i.e. the nerve when faradized caused no muscular contractions, but the muscles responded vigorously to direct excitation, hence the nerve was affected. The abdomen was then opened, and the trunks of the sciatic plexus excited, those going to the protected limb evoked strong contractions of the muscles below the ligature, but the nerves of the opposite side caused no contractions in the unprotected leg; hence the trunks of the nerves are not paralyzed when their terminations are. A little later, it was found that stimulation of the skin of the trunk induced only weak and slowly developed contractions of the protected leg; thus showing that the afferent nerves and the reflex functions of the cord were not abolished. From the weak character and slow development of these contractions, it was inferred that either the afferent nerves or the cord were depressed. The spinal cord was then divided, and the posterior part stimulated; only weak contractions were induced in the protected limb, showing that the cord although not paralyzed, yet had its conducting power impaired.

In about an hour after the injection, the muscles of the unprotected leg contracted feebly and rather slowly, on direct excitation, whilst those on the protected side still responded vigorously, thus showing that in larger doses the drug is a muscle as well as a nerve poison. The heart

was found to be weakened, and stimulation of the vagus produced no inhibition.

Smaller doses than those mentioned above are quite sufficient to produce the characteristic effects; thus 2 mgrms. injected subcutaneously quite paralyzed a large female frog (distended with ova) weighing 88·5 grms, and when these smaller doses are used, the order in which the effects are produced is much better seen.

Voluntary movements and reflex actions disappear first, and the former before the latter, whilst the muscles still respond on nerve excitation; then this disappears and then the contractions evoked by direct excitation are weakened, but unless the dose injected be large, the muscles do not cease to respond to direct excitation, and so it is only in comparatively large doses that the drug is a muscle poison.

As mentioned above, Ulexin in the frog causes weakening and slowing of the cardiac beats, and paralyzes the vagus so that stimulation of this nerve is inefficacious, although direct stimulation of the sinus still produces arrest. The same phenomena are much more readily seen in the eel, where as shown by M'William, inhibition is readily produced reflexly by stimulation of the branchiae, tail, peritoneum etc. In the eel, after the injection of Ulexin into the peritoneum, the heart is found to be markedly weakened and slowed; and inhibition cannot be produced either reflexly by stimulation of the branchiae, etc., or by direct stimulation of the vagus itself, although previously to the injection of the drug, such stimulation was followed by prolonged standstill of the heart.

Hence Ulexin both in the frog and eel paralyzes the vagus and the motor nerves somewhat in the same manner as curare. The action of the drug on the respiration of the frog remains to be considered, and this is quite unlike anything produced by curare. This, which is the most powerful action of the drug, is seen when it is given in very small doses. In a frog weighing 30 grms., 1 cc. of a solution of a strength of 1 in 300 was injected at 9.20 a.m.: at 9.50 the respirations were impaired, there being long intervals without any, and then a series of short and superficial respiratory acts. At this time the animal could hop about perfectly, and the corneal reflex was still present. At 10.15 a.m. the respirations were occasional and shallow, and there were marked occasional quivering movements of the thoracic and abdominal muscles. At 2.50 p.m. the frog had quite recovered its voluntary power, but the respirations were still infrequent. This observation shows that the drug acts powerfully on the respiratory mechanism, in doses which only

produce a slight and transient paralysis of voluntary movement; and these doses also produce quivering movements of the voluntary muscles. With larger doses the respirations will be arrested some time before voluntary movement is paralyzed.

Pinet (*loc. cit.*) apparently concluded that in the frog the action of Ulexin was mainly on the nervous system, and concludes that the twitchings observed with small doses are of central origin. Certain experiments mentioned below on the mammal, would seem to throw some doubt upon this. Finally, besides the action of the drug on the motor nerves, it is seen that it paralyzes the vagal terminations, and that the activity of the respiratory centre is also abolished, but the latter action is best studied on the mammal.

2. Action of Ulexin Hydrobromate on the Mammal.

Observations were made in the cat and dog on the blood pressure, the respiration, and the kidney, and in all cases these results have been recorded. The respirations were recorded by a T piece in the trachea, the kidney was investigated by means of Roy's oncometer, the urine being recorded at the same time, and for the blood pressure a mercurial manometer was used. In the kidney experiments, the blood pressure was observed simultaneously. Solutions of the drug were injected into the external jugular vein, the animal being under chloroform only, but in the experiments on the kidney, the animal was also curarized and artificial respiration kept up. Curare was really unnecessary, as the Ulexin injected was sufficient to completely paralyze the animal, but owing to these kidney experiments having been made before the others this fact was not then known.

In the mammal Ulexin is a powerful respiratory poison, the intravenous injection of 3 mgrms. in a chloroformed cat, weighing 5 lbs., killing the animal with convulsions, in from two to three minutes; but if artificial respiration be kept up, the animal can be kept alive just as with curare. In a cat under chloroform, where the respiratory movements were being recorded, 5 mgrm. of Ulexin had the following effect. Before the injection, the respirations were at the rate of 26 per minute. Immediately after the intravenous injection of the drug, the respiratory acts were quickened to 40 in the minute, and were enormously increased in depth; much more so in fact than in rate, the amplitude of the respiratory curve being three or four times as great as normal. A further dose of 1·5 mgrms. was then injected, and this absolutely arrested the respiration, causing first however an attack of convulsions.

Artificial respiration was then kept up, and the animal thus kept alive, a blood pressure experiment being made; but even after nearly three hours there were no spontaneous respirations, and the artificial respiration being then stopped, the animal died. After the intravenous injection of Ulexin in the above doses, or subcutaneously in larger doses, a peculiar quivering, due to fibrillar contraction of the voluntary muscles, is seen for some time after all respiratory movements have ceased, and even when artificial respiration is kept up. These movements are not seen after large doses. Curiously enough they persist, after the part in which they are present has been completely severed from the body, and in one instance they persisted for as long as ten minutes in the completely detached fore limb of a cat. These muscular movements are not seen after large doses, and they are also not seen in curarized animals. Hence they are the effect of small and initial doses, and they seem to be somewhat similar to those described above, as occurring in the frog after small doses. Further, after the injection of small doses of Ulexin, the muscles respond to mechanical excitation much more readily than normally. If large doses be injected, i.e. 100 mgrms. and artificial respiration be used, it will be found that the muscles no longer respond, when the nerve going to them is stimulated, and that ultimately they only respond feebly to direct electrical excitation. Thus the drug acts first as a stimulant, and then as a depressor of the respiratory mechanism, and in larger doses paralyzes the motor nerves; but this effect is preceded by a period, during which the excitability of the voluntary muscles is increased, and during which quivering movements are produced, apparently of peripheral origin.

As regards the action of the drug on the general blood pressure, Ulexin, both in curarized anaesthetized animals, and in non-curarized animals, in small doses, raises arterial tension very considerably; in some cases in fact, it almost doubles the height of the blood pressure curve for a short time.

Thus, in one case, the blood pressure measured in the carotid of a dog was equal to 7 inches of mercury, prior to the injection of 5 mgrms. of Ulexin intravenously. 25″ after this injection the pressure had risen to 10 inches, at which height it remained for exactly one minute, and then gradually fell to normal in another minute; ultimately falling to 5·5 inches, at which height it remained. Thus the drug first causes a rapid, but great rise of arterial pressure of short duration; followed by a gradual, persistent, but slight fall. If larger doses be injected, i.e. 50 mgrms., the rise of pressure is very slight, whereas the subsequent fall

is greater, and also of longer duration. By taking simultaneous curves of the blood pressure and of the kidney (with the oncometer), it is seen that synchronously with the rise of general blood pressure, there is a marked contraction of the kidney. It is probable that this peripheral constriction is general, and that this is the cause of the rise of blood pressure.

After division of the spinal cord below the medulla (in dogs), Ulexin still causes a marked rise of pressure, and thus the effect is not at any rate solely due to stimulation of the medullary vasomotor centre.

During the rise of pressure, the heart is very much accelerated; thus, in the case quoted above, the heart was beating at the rate of 144 per minute, before the injection; this was increased to 216, fifty seconds after the injection. Along with this acceleration, there is a marked diminution in the force of the cardiac beats. This accelerating effect is preceded by a very short period, immediately following the injection, when the heart beat is slowed and increased in force. This acceleration of the cardiac beat is still observed after section of both vagi. Thus in one case, in a cat, the heart was beating at the rate of 150 per minute; 5 mgrms. of Ulexin raised it to 228; some time after, when the rate had again become normal, the vagi were divided, the rate then rose to 168 per minute, the same dose of Ulexin increased this to 216.

With large doses the force of the heart is greatly weakened, and the fall of blood pressure produced is considerable; but, even when 25% solutions are used, the drug will not kill through the heart for a considerable time if artificial respiration be kept up.

After the injection of Ulexin, stimulation of the vagus does not cause inhibition as normally, but this paralysis of the vagus is rather transitory; so that, if a short time is allowed to elapse between the injection and the nerve excitation, the latter will cause a slight inhibition. If large doses are used the paralysis of the vagus is complete.

Ulexin produces a powerful effect on the kidney, as estimated by the oncometer. Doses of 5 mgrms. produce a marked constriction, followed by a very large expansion of short duration. If large doses are repeatedly injected, the drug no longer causes any constriction, but only a slight dilatation, so that as a rule the greatest constriction is produced by the first dose. In connection with this point, we saw that the rise of blood pressure is also not observed, when large doses are frequently repeated, and it is interesting to observe how the two sets of observations agree. The expansion of the kidney vessels produced by Ulexin, although frequently greater than that produced by caffein, is not so

persistent in its duration. Occasionally the effect on the kidney is a little more complicated, the injection being followed by a transitory expansion, lasting a few seconds; this being followed by a contraction, and finally the kidney expanding a second time.

As regards the effects of Ulexin on the urinary flow, both the effect on the general blood pressure and on the kidney circulation would point to its being a diuretic, and this is what is found. In three successive observations made on the same dog under chloroform and curare, the following were the results obtained. Previously to the injection of the drug, the flow was at the rate of 3 drops a minute, after 10 mgrms. of Ulexin, the rate was increased to 12 a minute; but this effect was only maintained for one minute. The flow then fell to 3—4 drops a minute, that is to say returned to normal; 50 mgrms. of Ulexin then quickened the flow to 9 drops a minute, at which rate it remained for two minutes. A second dose of 50 mgrms. then increased this rate to 12 per minute, and this was maintained for several minutes. Thus Ulexin is a powerful diuretic, as it quadrupled the urinary flow; but as is seen, the effect of small doses, such as 12 mgrms. is transitory, and it required as much as 100 mgrms. to maintain it for any length of time. Thus although the diuretic effect is quite as great, if not greater than that of caffein, the diuresis produced by the latter goes on for a much longer time. Further the doses of Ulexin necessary to maintain the diuretic effect would kill through the Respiration. Thus Ulexin is an alkaloid, having a powerful and wide spread action, being a nerve and muscle poison, a respiratory poison, raising arterial tension and producing diuresis; but the respiratory action of the drug, being produced by the smallest doses, seems to be the most important.