J. Physiol. (1961), **157**, *pp.* 565–580
With 6 text-figures
Printed in Great Britain

SOME FACTORS CONCERNED IN DIFFERENTIAL NERVE BLOCK BY LOCAL ANAESTHETICS

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(*Received* 6 *February* 1961)

The differential blocking of nerve fibres of different sizes by local anaesthetics was first investigated by Gasser & Erlanger (1929). They found that within the A fibre group of nerves of the frog and the dog, cocaine blocks fibres of smaller diameter and slower conduction rate before larger fibres; but as they found that 'blocking of some of the fast fibres occurs before the slow ones', they were unable to formulate a satisfactory theory to account for all the facts they observed.

The subject was re-investigated by Heinbecker, Bishop & O'Leary (1934) using procaine; and they also found that 'blocking is not complete in the slower somatic group before definite depression, from 30 to 50%, is also present in the faster groups'. They concluded 'that the order of depression of the fibres is in general in the inverse order of the diameter of the fibres, but that other factors may be involved, such as the character of the axon and the thickness of the myelin sheath'. Leksell (1945) found that ethocaine (procaine) has a greater effect on the gamma fibres than on the alpha fibres of the anterior roots, and it was later found by Matthews and Rushworth (1957) that procaine blocks gamma fibres before alpha fibres. On the other hand, Everett & Goodsell (1952) stated that C fibres or 'small slow nerve fibres' are not more sensitive to procaine than 'the large fast A fibres', and Everett & Toman (1954) found that 'A and C groups' were often blocked at the same time.

Apart from considerations of fibre size and of the presence or absence of myelination, it has often been stated that sensory nerve fibres are more susceptible to the action of local anaesthetics than motor fibres. MacIntosh (1957), for instance, states: 'It is well known that in local and spinal analgesia, sensory nerve fibres are affected before motor.' This view seems to be based on early observations, such as those of Dixon (1905), that cocaine applied to a nerve supplying a muscle blocks reflex contractions before it blocks contractions due to electrical stimulation of the nerve. Recent work by Matthews & Rushworth (1957), however, has provided an

alternative explanation; for it now seems probable that the disappearance of the reflex effects is due to selective blocking of the small motor (gamma) fibres, while the contraction due to nerve stimulation remains as long as the alpha fibres remain unblocked.

The present paper reports observations on the effects of local anaesthetics on conduction in fibres of the spinal roots; on the order of block within the A group of fibres; and on the order of block of the non-myelinated fibres compared to the myelinated. Further, it elucidates some of the factors giving rise to differential blocking; and it proposes an explanation of the inconsistency concerning blocking of fibres of different sizes.

METHODS

The methods are essentially the same as those given in a previous paper (Nathan & Sears, 1960*a*). The experiments were performed on a total of 22 cats, anaesthetized with Nembutal (pentobarbitone, Abbott Laboratories; 35–40 mg/kg) given by intraperitoneal injection. In all the experiments the local anaesthetics were applied to the nerve roots. The lumbosacral roots and various nerves of the hind limb and tail were made available for stimulation or for recording. For studying the effects of the anaesthetics on the A fibres of the posterior roots the stimulating electrodes were applied to the roots and the recording was made from the peripheral nerve; as the peripheral nerves were divided distally, this recording of antidromic conduction produced records free from spontaneous afferent impulses without the need of widespread de-afferentation. In experiments on anterior roots both orthodromic and antidromic conduction were used. For studying the effects of anaesthetics on the C fibres, the limb-nerve preparations were unsuitable, owing to the excessive temporal dispersion of the impulses over the conduction distances encountered. It was found that the roots innervating the tail formed a suitable preparation. The laminectomy was continued to the proximal vertebrae of the tail, which exposed suitable lengths of roots ensheathed by dura mater. The roots were divided distally close to their intervertebral foramina and were placed on stimulating electrodes; the corresponding posterior roots were cut close to the spinal cord, passed through the chamber (described below), and placed on recording electrodes. In this preparation the conduction distance is shorter than in the limb-nerve spinal root preparation, and as stimulation and recording is from the same root, divided at each end, the recording is free from spontaneous afferent impulses from the periphery.

The stimulating and recording methods were the same as those used previously, except that square-wave voltage pulses were used for stimulating the C fibres, whereas previously condenser discharges had been used. The stimulator output was fed through a four-position selector switch to one of four separate potentiometers. At the beginning of an experiment each potentiometer could be adjusted to provide a stimulus, the intensity of which was adequate to excite only large fibres or both large and small fibres, according to the requirements of the experiment. It was thus possible during an experiment to select quickly a pre-set stimulus intensity which was known only to excite fibres of a given conduction rate; this procedure allowed a comparison to be made between the selective activation of the fibre group by electrical stimulation and the degree of differential blocking caused by the local anaesthetic. In all experiments the stimulus repetition interval was 1 sec.

In designing a chamber for the application of the solutions the ability of the impulse to 'hurdle' two or three inactive nodes was taken into account. According to Visozo & Young (1948) the longest internode of mammalian fibres is 1·5 mm. The internal diameter of the chamber used was 8 mm; and therefore it contained at least 5 nodes of the largest fibres. The chamber, made of Perspex, is illustrated in Fig. 1. Its cubic capacity is 1 ml. The

filament of nerve root was passed through the holes on either side of the chamber; this was carried out by tying a thread of fine silk to the cut end of the filament, threading the silk through a fine needle, and passing the needle through the holes in the chamber. The chamber was then placed deep in the trough formed by the laminectomy, in such a position that the hole on one side of the chamber was close to the region where the root passes through the dura mater. The silk was then gently pulled so as to draw as great a length as possible of the root through the chamber, without causing it to be kinked or pressed on; low-power magnification was used to control this procedure. The circular channel of the chamber was then packed with soft wax, which was firmly pressed round the nerve root, so as to make the

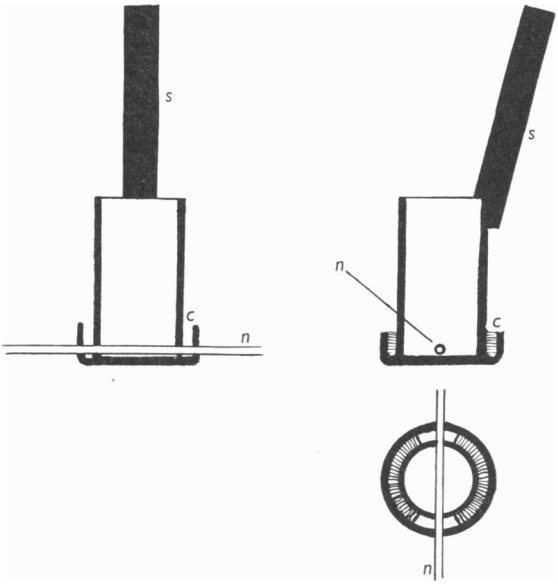

Fig. 1. Elevation and plan views of Perspex chambers; *c*, channel—shaded part is the part filled with Perspex cement; *n*, filament of nerve root passing through chamber; *s*, supporting rod.

junction between the hole and the root watertight. The wax was made from a mixture of paraffin wax (m.p. 56° C) and white soft paraffin, melted, mixed together, and allowed to cool. The proximal end of the root was placed on platinum electrodes supported near the chamber. If sampling then showed that the preparation was satisfactory for displaying both the fast-conducting and slowly-conducting fibres (which is not always the case), the entire trough formed by the laminectomy was covered by paraffin oil equilibrated with oxygen and carbon dioxide. The Perspex chamber which projected above the level of the paraffin oil was filled with Ringer–Locke solution.

The local anaesthetics used were cocaine, procaine and lignocaine. They were dissolved either in Ringer–Locke solution or in a modified Krebs–Henseleit solution. The Ringer–Locke solution had the following composition (mM): NaCl, 145; KCl, 5·7; $CaCl_2$, 2·2; $NaHCO_3$, 2·1; glucose, 5·5. The Krebs–Henseleit solution was closely similar to that modified by Diamond, Gray & Inman (1958), and had the following composition (mM): NaCl, 145; $CaCl_2$, 2·5; $MgSO_4$, 1·2; KH_2PO_4, 0·58; K_2HPO_4, 2·5; glucose, 5·5. This solution differed from that of Diamond *et al.* in that no HCl was added to it. The reason for using this solution was that some of the experiments reported here were done in conjunction with experiments

on the differential blocking induced by sodium-deficient solutions (Nathan & Sears, 1960*b*). The pH of the solutions was tested on a pH meter and was found to lie between 7 and 7·4. Before use they were equilibrated with 5 % CO_2 and 95 % O_2.

The nomenclature used here for labelling the fibre groups combines various current usages. Thus, following Erlanger & Gasser (1937), the A fibres conducting at 80–120 m/sec are called alpha fibres, those conducting from 60 to 80 m/sec are called beta, those conducting from 40 to 60 m/sec are called gamma, and those conducting at rates of less than 40 m/sec are called delta. The term 'fast-conducting' applied to the nerve fibres of the lumbosacral roots refers to the alpha and beta fibres, such as those supplying the extrafusal muscle fibres. The small fibres of the anterior root are referred to in the literature as either the small-fibre groups or as the gamma group. Here they will be called the gamma-delta fibres, because their conduction rates were found to be between 15 and 50 m/sec, with a peak at 30 m/sec. This same range was found by Kuffler, Hunt & Quilliam (1951). In the tail-nerve preparation the fastest conducting fibres were found to be in the gamma range.

RESULTS

Differential rate of blocking of fibre groups

When local anaesthetics are applied to spinal roots, the constituent nerve fibres are blocked at times which are related to their conduction rates; yet some of the faster-conducting fibres are blocked at the same time as some more slowly-conducting fibres. This form of differential blocking was found in all experiments when the concentration of anaesthetic was 0·1 % or higher. A typical experiment showing this form of differential blocking is illustrated in Fig. 2. Procaine 0·1 % in modified Krebs–Henseleit solution was applied to the first sacral posterior root; the root was stimulated and the recording was made from the sciatic nerve. The conduction rate of the fibres (measured to the peaks of the waves) was 80 m/sec for the alpha group, 65 m/sec for the beta group, and 12–19 m/sec for the delta group. The records on the left display the action potentials of the fast-conducting fibres, and those on the right display the action potentials of the slowly-conducting fibres. The latter consist of 10 superimposed sweeps: 5 sweeps were recorded at a stimulus intensity which, before the application of the procaine, had been adjusted to be below threshold for the delta group; the other 5 sweeps were recorded at a stimulus intensity giving a maximal response of this group of fibres.

Within 45 sec of filling the chamber with 0·1 % procaine in modified Krebs–Henseleit solution the wave of the delta group was considerably reduced. The height of the alpha spike at this time was diminished by 4 %; the beta wave, which in the control record appears as the notch in the descending phase of the alpha spike, was diminished by 20 % of the original height of the notch on the alpha spike. By 2 min 15 sec the delta wave had gone, to the extent that the record was barely distinguishable from that obtained with the stimulus intensity set below threshold for these small fibres; at this time the alpha spike was reduced by 8 %. The

fall-out of the delta wave can also be seen in the records taken at low amplification. At 4 min 45 sec the alpha spike was reduced by 24 % of its original height and at 6 min 45 sec by 40 %.

This experiment demonstrates that at a time when all the slowly-conducting fibres were blocked a proportion of the fast-conducting fibres was

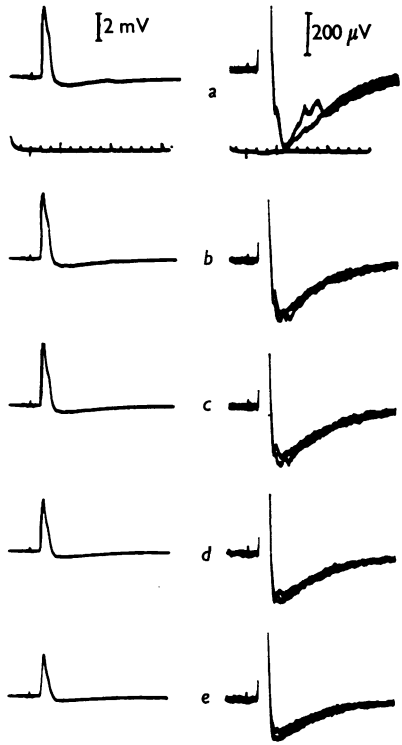

Fig. 2. Effect of 0·1 % procaine in modified Krebs–Henseleit solution on conduction in A fibres. Left-hand column, low amplification, to show fast-conducting fibres (alpha-beta), 5 sweeps superimposed. Right-hand column, high amplification, to show slowly-conducting fibres (delta), 10 sweeps superimposed; 5 of the sweeps made with stimulus intensity below threshold for slowly-conducting fibres. Records at the two different amplifications were made one immediately after the other; the time stated is that of the middle of the recording period. *a*, before application of procaine; *b*, *c*, *d*, *e*, 45 sec, 2 min 15 sec, 4 min 45 sec, 6 min 45 sec after application. Time marker, 1 and 5 msec intervals.

still conducting; it also shows that some of the fast-conducting fibres were blocked early, although subsequently the rate of blocking of this group was slower than that of the slowly-conducting fibres. This form of differential blocking, in which one or more groups of fibres tend to be blocked more rapidly than others and in which eventually all fibres are blocked, we shall refer to as *differential rate of blocking*.

It is of interest to note that when local anaesthetics are applied to spinal roots blocking of some of the fibres occurs just as quickly as it does when anaesthetics are applied to isolated single nerve fibres or to de-sheathed peripheral nerves, that is, within seconds of applying the solution.

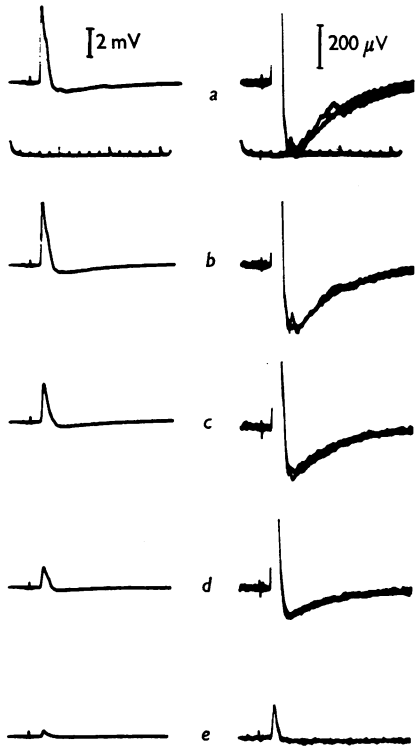

Fig. 3. Effect of 0·5 % procaine in modified Krebs–Henseleit solution on conduction in A fibres. Left-hand, low amplification, 5 sweeps superimposed. Right-hand, high amplification, 5 sweeps below threshold, 5 sweeps maximal for delta fibres. *a*, before application of procaine; *b*, 5–10 sec; *c*, 1 min 5 sec; *d*, *e*, 1 min 55 sec, 3 min after application. Time marker, 1 and 5 msec intervals.

The effect of applying a higher concentration is shown by the experiment illustrated in Fig. 3. Procaine 0·5 % in modified Krebs–Henseleit solution was applied to the same root as was used for the experiment illustrated in Fig. 2. By comparing Figs. 2 and 3 it is seen that 5–10 sec after applying this higher concentration of anaesthetic the delta wave was reduced by an amount similar to that occurring 45 sec after applying the weaker concentration. The alpha wave in Fig. 3, recorded within the next 5 sec, had already fallen by 12 %. The record taken at 1 min, with the higher concentration of anaesthetic, showed no trace of the delta wave, while the alpha wave, recorded a few seconds later, showed a reduction

of 46 % of its original height. At 1 min 55 sec the alpha wave was reduced by 74 % and by 3 min only a trace of it remained. It can be seen that, at a time when the height of the delta wave was reduced by similar amounts in the two experiments, with the low concentration of anaesthetic the reduction in the alpha wave was 4 % and with the high concentration it was 12 %. And when in both experiments the delta wave had gone, with the low concentration the reduction in the alpha wave was 8 % and with the high concentration it was 46 %. It is concluded from these two experiments and 11 others (9 with procaine and 2 with cocaine), in which the differential effect of two different concentrations of the same anaesthetic was examined on the same root, that the greatest degree of differential blocking occurs with weaker solutions.

In one respect the results obtained from applying the anaesthetics to spinal roots seem to differ from those observed when they are applied to peripheral nerves. Those working on peripheral nerves, for instance Matthews & Rushworth (1957), observed soon after the application of the anaesthetic a temporary phase during which there was blocking of most of the small fibres without blocking of many of the large fibres; this phase was followed eventually by blocking of all the large fibres. It was in this sense that Gasser & Erlanger (1929) stated 'small fibres were blocked before large ones'. But when the anaesthetic is applied to spinal roots, blocking of some large and of some small fibres occurs early and simultaneously, although subsequently the blocking of the fibres as a group still occurs at a differential rate.

Absolute differential blocking of fibre groups

Myelinated fibres. The question next arises whether there are concentrations of anaesthetics that will selectively block all small fibres without blocking the larger fibres. The effects of applying a low concentration of anaesthetic to an anterior root and then increasing the concentration are illustrated in Fig. 4. The nerve to the hamstrings was stimulated, and recording was made from the first sacral anterior root. The conduction rates of the fast-conducting fibres was 70 m/sec (measured to the peak) and of the slowly-conducting fibres was from 18 to 35 m/sec. The first concentration of procaine in modified Krebs–Henseleit solution applied was 0·03 %. After this solution had surrounded the root for 21 min, the wave due to the slowly-conducting fibres was slightly modified in form and both its components showed some reduction in height; the latency to the foot of the wave was increased by 0·2–0·3 msec. After 22 min this solution was replaced by a 0·04 % solution. After this solution had been applied for 18 min, with no further changes of the slowly-conducted wave and no effect on the fast-conducted wave, it was replaced by a 0·05 % solution. After

this solution had surrounded the root for 15 min the height of the wave of the fast-conducting fibres still remained undiminished; there was a further slight alteration in form of the slowly-conducted wave and a further increase in its latency, but it may be seen that the majority of the fibres of this group were still conducting. When this solution was replaced 2 min later by a 0·06 % solution of procaine there was a rapid decrease in

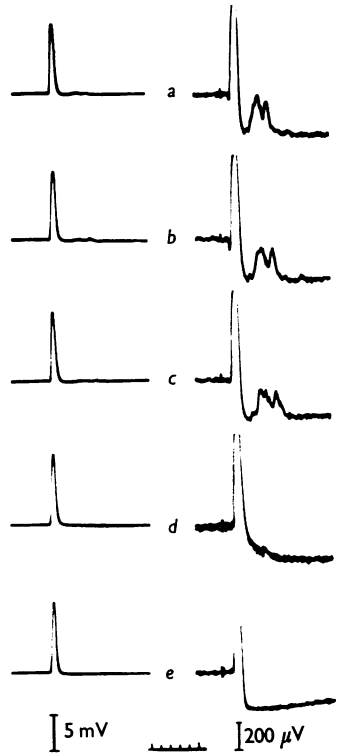

Fig. 4. Effect of 0·03, 0·05 and 0·06 % procaine in modified Krebs–Henseleit solution on conduction in A fibres. Each record consists of 5 superimposed sweeps. *a*, before application of procaine; *b*, 21 min after application of 0·03 % procaine; *c*, 15 min after application of 0·05 % procaine; *d*, 19 min after application of 0·06 % procaine; *e*, 62 min after application of 0·06 % procaine (120 min after application of the first procaine solution). Time marker 1 and 5 msec intervals.

amplitude of the slowly-conducted wave. Nineteen minutes after applying the 0·06 % solution only a trace of this wave was seen, whereas the fast-conducted wave remained unaltered. At the final observation, made 62 min after the application of the 0·06 % solution (120 min after the start of the experiment), there was no change in the fast-conducted wave; but all trace of the slowly-conducted wave had gone.

In this series of experiments, the concentration of the anaesthetic must have been adequate throughout the root to block all the smaller myelinated fibres present; yet such a concentration has failed to block the larger fibres. This form of differential blocking we shall refer to as *absolute differential blocking.*

The concentrations of anaesthetic that give absolute differential blocking of the gamma-delta group while leaving the alpha-beta group unaffected have been found to be fairly constant. The exact concentration, however, differs according to whether the solvent is Ringer–Locke solution or modified Krebs–Henseleit solution. The former solution behaves as if there is more procaine base available, which may be due to small differences in the pH of the two solutions. With regard to the concentrations needed to block the small fibres of the anterior roots without blocking the large fibres, it has been found that procaine at a concentration of 0·01 % in either solution has no effect on conduction of either group of fibres. At a concentration of 0·02 % slowing in the conduction rate of the gamma-delta group is seen, but there is no reduction in the amplitude of the action potential; there is no effect on conduction of the alpha-beta group. Procaine in Krebs–Henseleit solution at concentrations of 0·03–0·06 % causes progressively increasing slowing in conduction rate combined with blocking of the fibres of the gamma-delta group, the 0·06 % solution blocking all fibres of this group. These concentrations have no effect on the alpa-beta fibres. The corresponding concentrations of procaine in Ringer–Locke solution for blocking the gamma-delta group without affecting the alpha-beta group was found to be 0·04 % to 0·05 %.

When concentrations of anaesthetic are used that are just critical for a given group of fibres, following removal of the anaesthetic solution, recovery of conduction is rapid. For instance, in the experiment illustrated in Fig. 4, even though the small fibres had been blocked for 60 min, a proportion of them recovered within 2 min of replacing the anaesthetic by modified Krebs–Henseleit solution.

To determine the concentration of anaesthetic that is critical for blocking smaller delta fibres, experiments were done on the tail-nerve preparation; in these roots there is a group of delta fibres with a slower conduction rate than that of the delta fibres of the lumbar and first sacral anterior roots. An experiment typical of this series is illustrated in the left-hand column of Fig. 5. The conduction rate of the slowly-conducting group of delta fibres was 9·6–11·6 m/sec; the wave due to this group is seen as the large wave rising from the downstroke of the wave due to the fast-conducting fibres, the peak of which is off the record. Procaine 0·01 % in Ringer–Locke solution was applied. Within 2 min 40 sec the height of this wave had diminished by about 50 %; by 18 min the wave had gone.

Thus this concentration of procaine was critical or supra-critical for this group of small delta fibres; it did not affect conduction in the fibres with conduction rates around 40 m/sec. From experiments performed before this series on the more slowly-conducting delta fibres it had already been

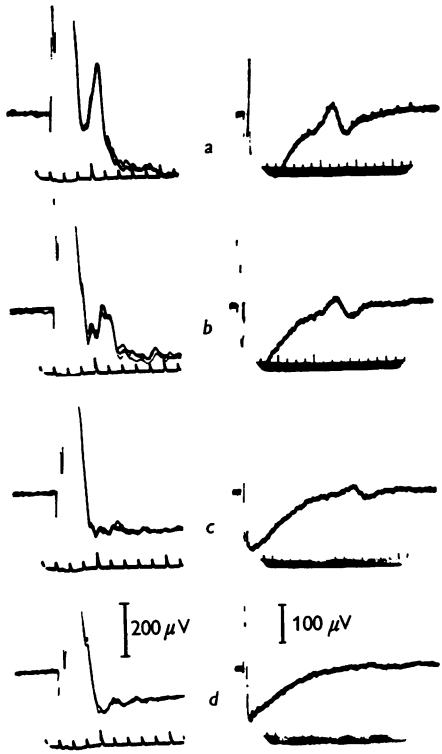

Fig. 5. Effect of 0·01 and 0·02 % procaine in Ringer–Locke solution on conduction in delta fibres and C fibres; delta fibres on left, C fibres on right. Delta fibres' component follows high-voltage spike of large fibres, which is off the trace at this amplification. Delta fibres record consists of 5 superimposed sweeps, C fibres record consists of single sweeps. *a*, before application of procaine; *b*, *c* (left-hand column), 2 min 40 sec, 18 min after application of 0·01 % procaine; (right-hand column), 2 min, 19 min after application of 0·01 % procaine; *d* (both columns), 30 sec after application of 0·02 % procaine. Time marker, 1, 5 and 20 msec intervals.

found that this concentration of procaine has no effect on conduction in larger, faster-conducting fibres.

Experiments on the tail-nerve preparation with cocaine gave similar results. It was possible to block all fibres with a conduction rate of 11–14 m/sec or less without blocking conduction of fibres conducting at rates around 40 m/sec. The concentration of cocaine that is just critical for these smaller fibres is 0·02 % in Ringer–Locke solution; concentrations slightly

higher than this, block fibres with conduction rates between 30 and 40 m/sec.

Myelinated and C fibres. The next question which arises is whether there are critical concentrations for the C fibres that block their conduction without affecting the myelinated fibres of the A group.

Before illustrating experiments that answer this question, mention must be made of the marked slowing of conduction rate that occurs in the C fibres with low concentrations of anaesthetics. This slowing in conduction rate is combined with blocking of many of the fibres. The combination of blocking and slowing in conduction rate causes an alteration in the form of the C fibres' action potential, and this makes a quantitative estimation less reliable than in the case of the myelinated fibres.

For the investigation of absolute differential blocking of C fibres, most experiments were done on the tail-nerve preparation; the concentrations of anaesthetic tested were those that we had found were critical for blocking conduction of the small myelinated fibres.

The effects of a low concentration of anaesthetic on conduction in the C fibres is illustrated in the right-hand column of Fig. 5. In this experiment, procaine 0·01 % in Ringer–Locke solution was first applied and it was followed later by a 0·02 % solution. The slowing of conduction rate of the C fibres can be seen: in the control records, the latency to the peak of the C fibres wave was 49 msec; after the root had been 2 min in procaine 0·01 %, it was 55 msec, and after 19 min, it was 64 msec. This slowing in conduction rate was associated with blocking of a large proportion of the fibres, as judged by the area of the wave. Increasing the concentration of procaine from 0·01 to 0·02 % caused complete block of all the C fibres.

To compare the concentrations of anaesthetic that are critical for C fibres and critical for small myelinated fibres, one may compare the records in the right- and left-hand columns of Fig. 5, for they are a typical example. It will be seen that procaine 0·01 % in Ringer–Locke solution blocked delta fibres with a conduction rate of 9·6–11·6 m/sec, and slowed conduction and blocked a large proportion of the C fibres. Most of the fibres of these two groups were blocked simultaneously. Doubling the concentration of procaine rapidly blocked the rest of the C fibres.

It was concluded from this and other experiments of the same type that concentrations of anaesthetic just sufficient to block the C fibres also block small delta fibres; but they are insufficient to block the larger delta fibres, or the gamma, beta or alpha fibres. The concentrations found that caused this absolute differential blocking were 0·01 % for both procaine and cocaine in Ringer–Locke solution.

In all experiments on the small myelinated and the C fibres it was found that the smallest, most slowly-conducting delta fibres present in the tail-

nerve preparation were blocked more rapidly than the C fibres. An experiment demonstrating this is illustrated in Fig. 6. In this tail-nerve preparation there were two groups of fibres with conduction rates in the delta range; their rates were 9–10 and 5–5·5 m/sec. They are seen as the two waves in the centre and later parts of the sweep following the wave due to the large fibres, the peak of which is off the record. The record made 3 min 50 sec after the application of procaine 0·01 % in modified Krebs–Henseleit

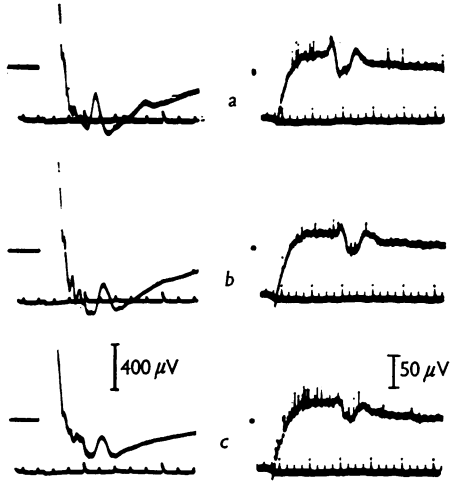

Fig. 6. Effect of 0·01 % procaine in modified Krebs–Henseleit solution on conduction in two groups of delta fibres and C fibres; delta fibres on left side, C fibres on right. Delta fibres record consists of 5 superimposed sweeps, C fibres record consists of single sweeps. *a*, before application of procaine; *b*, *c*, 3 min 50 sec, 5 min after application of procaine. Time marker, 1, 5 and 20 msec intervals.

solution shows all but complete obliteration of the wave of the most slowly-conducting delta fibres; it was abolished completely 5 min after application of the solution. By this time, the C fibres' action potential had been slightly altered in form and its latency increased from 47 to 53 msec. When the concentration of the procaine was increased to 0·02 %, the C fibres' action potential was rapidly abolished.

From such experiments it is seen that the generally accepted view of small fibres being blocked before large does not apply to a comparison between C fibres and the smallest myelinated fibres. For the smallest delta fibres are blocked with lower concentrations of anaesthetic than the C fibres; and when concentrations of anaesthetics adequate to block both groups are applied, the smallest delta fibres are blocked first.

It should be added that as the C fibres of the spinal roots are half the diameter of C fibres peripheral to the posterior root ganglia (Gasser, 1955).

it may well be that C fibres of peripheral nerves are not blocked with the same concentrations of anaesthetic and not in the same order with regard to the small myelinated fibres as the C fibres studied here. It may be that in peripheral nerves they are blocked simultaneously with larger delta fibres than those shown here and that they require higher concentrations of anaesthetic to block them.

DISCUSSION

We have found, like most investigators of this problem, that small myelinated fibres are more susceptible to the action of local anaesthetics than large; this is manifest as a differential rate of blocking of the fibres. But we find that this order of blocking holds only within the group of A fibres. Non-myelinated fibres are not the most susceptible of all fibres to the action of local anaesthetics; the smallest fibres of the A group are blocked earlier and with lower concentrations of anaesthetic than the C fibres. It has been established in addition that there are critical concentrations of local anaesthetics that block conduction in fibres of one size while leaving fibres of larger size still conducting. This form of selective blocking we have called absolute differential blocking.

The disclosure of absolute differential blocking may be attributed to two factors, the application of the anaesthetic directly to the spinal roots and the use of low concentrations of anaesthetic. The absence of significant barriers to diffusion in the spinal roots allows the concentration of anaesthetic to become uniform fairly rapidly throughout the root.

The fact that some of the large fibres are blocked at the same time as the small fibres has been interpreted by various workers as indicating that myelinated fibres do not fall out on a fibre-size basis. In peripheral nerves, on which most previous work was done, the sheath is known to act as a barrier to diffusion. As the concentration of anaesthetic within the sheath rises small fibres would be blocked before large; but as the concentration of anaesthetics used by previous workers, including ourselves (Nathan & Sears, 1957), have been 'supra-critical' for all groups of fibres, the larger fibres would eventually also be blocked; though at any time a large proportion of smaller fibres and a small proportion of larger fibres would be blocked. That is the situation of differential rate of blocking. Further, local variations in the concentration of anaesthetic within the sheath, due to differences in the diffusion pathway for different nerve bundles, and also to the possibility of local damage to the sheath during the preparation of peripheral nerves, would also lead to blocking of some large fibres before all the small ones were blocked.

It is well known that during recovery from the effects of a local anaesthetic the small fibres recover last and the large fibres first. The fact that

this order is the reverse of that for blocking fibre groups constituted the final argument for Gasser & Erlanger (1929), that a hypothesis of differential blocking based on chemical combination of the anaesthetic with the protoplasm of the fibres is untenable; for, to quote their words, 'since the surface per unit volume increases directly as the diameter decreases, the smaller the fibre the greater the accessibility', and this would lead to small fibres being both blocked and unblocked before large. The fact of there being different blocking concentrations of anaesthetic for the different sizes of fibres explains the order of recovery; for when the anaesthetic is diluted a subcritical concentration for the large fibres is achieved before that for the small.

It is necessary now to relate what is known of the mechanism of the action of anaesthetics on conduction to the differences in structure and function of the different groups of fibres. The effect of a local anaesthetic on a single myelinated fibre of the toad, as shown by Tasaki (1953), is to reduce the amplitude of the action current. In whole nerves or roots this diminution in current would be manifest as a reduction in the amplitude of the externally recorded compound action potential. This in fact was found by Kato (1924) and by Davis, Forbes, Brunswick & Hopkins (1926), who showed that impulses being propagated through a region of uniformly narcotized nerve do so at diminished amplitude. The mechanism of the reduction in action current by the local anaesthetic has been attributed, in the giant squid axon, to a reduction in the number of sodium carriers (Shanes, Freygang, Grundfest & Amatniek, 1959; Taylor, 1959), and in Purkinje muscle fibres to inactivation of the sodium carrier at high membrane potential (Weidmann, 1955). It would seem reasonable to assume that the electrical properties of the membrane of small and large myelinated fibres are the same; and that under the action of a given concentration of local anaesthetic the action current developed per unit of membrane would be reduced by the same amount. This would mean that whatever possible differences exist between the local circuits of small and of large fibres, due to the different internodal resistances and to the different areas of nodal membrane developing action current, a local anaesthetic would produce the same proportionate reduction in the total nodal action current. The fact of absolute differential blocking with critical concentrations thus suggests that the ratio of the action current developed to that necessary for propagation is different in fibres of different sizes. This ratio—the safety factor—was measured by Tasaki (1953) in large single myelinated fibres of the toad. We know of no figures for the safety factor of smaller toad nerves nor of small or large mammalian fibres.

The experiments carried out to investigate differential blocking between

C fibres and A fibres showed that, with low concentrations of anaesthetics, the myelinated fibres conducting at rates of approximately 10 m/sec were blocked simultaneously with the C fibres; with still lower concentrations, the very smallest myelinated fibres were blocked at a time when a large proportion of the C fibres was still conducting, although their conduction rate was slowed. These observations on the fibres of the cat's spinal roots do not support the usual view that the C fibres are the most susceptible to the action of local anaesthetics. Attempts to correlate the sensory dissociation found on injection of anaesthetics in low concentrations in man with the differential blocking of fibre groups will need some re-assessment.

In a review of the action of local anaesthetics Toman (1952) reported that in experiments on the rabbit's vagus 'a 1 mM solution of procaine depresses A fibres first and C fibres last'. Everett & Toman (1954) concluded that such results 'do not support the older concepts of nerve block based on fibre size'. In the experiment on the rabbit's vagus, quoted by Toman, the comparison is being made between A and B fibres; yet it is known that these somatic and autonomic myelinated fibres show certain different electrical properties (Grundfest, 1939). Further, when comparisons are made between myelinated and C fibres, one is comparing the effects of anaesthetics on two different modes of conduction, on saltatory and continuous conduction; it might be expected that anaesthetics would affect them differently. When a comparison is made of fibres having the same electrical properties and the same mode of conduction, it is found that anaesthetics affect the fibres as though they are a continuous series differing only in size.

SUMMARY

1. The effects of local anaesthetics on conduction in myelinated and non-myelinated fibres of the spinal roots of the cat have been studied.

2. Different concentrations of anaesthetic are required to block conduction in fibres of different sizes; the concentration necessary to block small fibres was found to be lower than that necessary to block large fibres.

3. Differential rate of blocking of fibre groups was obtained when the concentration of anaesthetic exceeded that necessary for blocking all fibres present.

4. The minimum concentration of anaesthetic for blocking non-myelinated fibres was found also to block the smaller myelinated fibres.

5. Still lower concentrations of anaesthetic blocked the very smallest myelinated fibres without blocking the group of non-myelinated fibres.

We take this opportunity of thanking Drs E. A. Carmichael and W. A. Cobb for facilities to do this work and for their help.

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