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The Response of Maximal and Submaximal Action Potentials from Frog Sciatic Nerve to 200 KV X-Rays

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THE RESPONSE OF MAXIMAL AND SUBMAXIMAL ACTION POTENTIALS FROM SCIATIC NERVE TO 200 KV X-RAYS

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The response of maximal and submaximal action potentials from frog sciatic nerve to 200 kV X-rays.

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ABSTRACT

Maximal action potentials (MAP) from isolated, frog sciatic nerve were recorded before and during X-irradiation. MAP amplitudes were not changed by 10 kR of 200 kV X-rays in 19 trials; in 16 other experiments the MAP amplitudes were not altered by 100 kR of X-irradiation. Sixteen nerves were irradiated until complete suppression of the MAP was evidenced, which required 300 kR (average) of X-rays. Rapid attenuation of the MAP amplitude was initiated with 160 to 200 kR of X-rays. Twelve nerves exhibited a 4 to 10% increase of the MAP amplitude prior to rapid attenuation; four other nerves revealed only decreases in the MAP amplitude with X-rays in excess of 160 kR. In these experiments the maximal threshold stimulus (MTS) to evoke a MAP remained unchanged below 100 kR of X-rays; during attenuation of the MAP amplitude the MTS increased.

The duration of the MAP increased in all nerves exposed to 20 kR of X-rays even though the MAP amplitude remained unaffected. In some cases 10 kR of X-rays provoked changes in the duration of the MAP.

Submaximal action potentials (SMAP) generated by 57 nerves were recorded before and during exposure to X-irradiation. The SMAP amplitude remained unchanged in 31 nerves (54.4%), increased in 20 nerves (35.1%), and decreased in 6 nerves when exposed to 10 kR of X-rays. These findings failed to support the claim that 10 kR of X-rays only heightened SMAP amplitudes. Nerves that always produced stable SMAPs during the control period were insensitive to irradiation. Nerves which exhibited a temporal increase or decrease in the SMAP amplitude during the preirradiation interval tended to be provoked into a similar SMAP amplitude change with 200 kV X-rays.

Key words: maximal and submaximal action potentials; nerve; X-irradiation.

INTRODUCTION

It was not clear if a relationship existed between the amplitude of the neural impulse and low doses of irradiation. Studies made before 1959 (1 to 5) indicated that the maximal action potential (MAP) of peripheral nerve was highly resistant to ionizing radiation. For instance, Gerstner (6,7) reported that only after nerve received 180 kR of X-rays did the MAP start to fall, and after absorbing twice this dose 15% of the MAP still was detectable.

A little over a decade ago Bachofer (8) was the first to record neural impulses during exposure to ionizing radiation. Bachofer (8,9) and Bachofer and Gautereaux (10,11) asserted that the MAP amplitude of nerve was regularly increased or enhanced with the onset of irradiation, and that simultaneously there was a decline in the electric threshold to stimulation. The view that MAP amplitudes were augmented by low doses of irradiation was encouraged by a number of reports (8 to 15).

Other information (16 to 21) either failed to corroborate the contention that low doses of irradiation consistently increased the MAP or frankly contradicted this assertion. Kroebel and Krohm (22) reported that 6 rads of alpha particle radiation decreased the MAP of nerve. A similar attenuation of the neural impulse was found after exposure to 60 R of X-rays (23).

From these reports it was uncertain whether low doses of ionizing radiation enhanced the MAP amplitude of nerves (8 to 13), attenuated the MAP (6,7, 17 to 23), or had no electrophysiologic effect (1 to 5). A further attempt was made to throw light onto this problem by exposing sciatic nerves to 200 kV X-rays.

Available information concerning the effects of irradiation on the submaximal action potential (SMAP) amplitude of nerve was also ambiguous. Seymour and

Dawson (20) stated that the SMAP amplitudes of nerves were heightened with only 100 R of X-irradiation, although this effect was considered to proceed from zero dose. Some studies (22,24,25) supported this view while other data (17,26,27) was in disagreement with the opinion that irradiation in low doses increased the SMAP amplitude of nerve.

In this paper the SMAP amplitudes served as a physiologic indicator when isolated sciatic nerves were exposed to 10 kR of X-rays.

METHODS

BIOLOGICAL PROCEDURE

Frogs (Rana pipiens), weighing about 35 grams, were used in these experiments. Each frog was decapitated and its spinal cord pithed. By careful dissection the sciatic nerves were removed, tied with surgical thread at each terminal, and stored in Ringer's solution (28). The excitable state of each nerve was assessed by placing an isolated nerve on Ag-AgCl electrodes in a moist chamber through which 96% air - 4% CO_2 could be circulated. The gas mixture passed through three water-filled gas-washing cylinders prior to entry into the nerve chamber.

ELECTROPHYSIOLOGICAL TECHNIQUES

One pair of Ag-AgCl electrodes in the nerve chamber served as an anode-cathode which sent to the central end of the sciatic nerve rectangular pulses 0.1 msec in duration at 20 l.p.s in most experiments. The voltage output from a stimulator (Grass, Model S-4 and isolation unit) was adjusted to produce a maximal action potential (MAP) or a submaximal action potential (SMAP). The action potential was detected by another pair of Ag-AgCl electrodes in contact with the peripheral end of the sciatic nerve. The leads from these elctrodes ran to a push-pull ac preamplifer (Grass, Model P-5) which delivered its signal to an oscilloscope (Tektronix, Model 532) with a high-gain differential input amplifier (Textronix, Type 53/54D). A multifunction stimulator (Grass, Model S-8), a low-level preamplifier (Textronix, Type 122), a storage oscilloscope

(Tektronix, Type RM 564) with a dual trace differential amplifier (Textronix, Type 3A3) and a time base plug-in-unit (Textronix, Type 3B3) were also employed. Action potentials from nerves were photographed as oscillograms using polaroid oscilloscope cameras (Du Mont, Model 302; Tektronix, Model C-12).

X-IRRADIATION PROCEDURE

A plastic, moist chamber containing a nerve mounted on Ag-AgCl electrodes was sealed with a 1 mil Mylar window. This chamber was placed under the exit port of a therapeutic X-ray machine. This machine was operated at 200 kV with a current of 15 ma; the oil immersing the X-ray tube was equivalent to an inherent filtration of 1.0 mm Al; added filtration consisted of a 0.5 mm Al plate, and 8.0 mm air path and the 1 mil Mylar window of the nerve chamber; the focus-to-target distance (FTD) was 13.6 cm. The HVL for the X-ray beam produced under these circumstances was 0.83 mm of Cu. The exposure rate delivered to the surface of the isolated nerve was 1,700 ± 8 R/min as detected with a Victoreen condenser ionization chamber.

Neural action potentials were monitored and recorded during irradiation in an adjacent, shielded room. The effects of 200 kV X-rays on 92 isolated sciatic nerves is discussed in this report.

RESULTS

MAXIMAL ACTION POTENTIALS

The stimulus strength delivered to nerve preparations was made just sufficient to evoke an action potential of maximal amplitude (MAP). This condition defined a maximal threshold stimulus (MTS).

About one minute before each action potential was photographed, the voltage from a stimulator was adjusted to be MTS and recorded. Thus, tested values for MTSs and MAPs were available for analysis.

In Fig. 1 is presented a composition of twenty MAPs from a sciatic nerve administered 2.8 kR of 200 kV X-rays. Neither the MAP amplitudes of this

irradiated nerve, nor the MTSs employed to generate MAPs were influenced by this exposure.

In 19 experiments isolated sciatic nerves were given 10 kR of X-rays. It was found that the MAP amplitude and MTS were insensitive to this exposure. These findings together with those to be detailed were in disagreement with reports claiming an immediate enhancement of the MAP amplitude and a decline in the electric threshold for excitation with the onset of irradiation (8 to 11).

Fig. 2 illustrates the effects of high exposures of 200 kV X-rays on the MAPs of a nerve. The same nerve was used to evoke MAPs in Figs. 1 and 2. There was no significant change of the MAP amplitude with continuous irradiation until 100 kR was approached. In Fig. 2 there was a 10% increase of the MAP amplitude with 130 kR of X-rays. The MAP amplitude declined rapidly with X-ray doses greater than 143.1 kR and inhibition of neural activity occurred near 300 kR. It was observed that the MTS increased during attenuation of the MAP amplitude.

The "relative" amplitude, duration, and detection period of MAPs of Figs. 1 and 2 were plotted as a function of the X-ray exposure in Fig. 3. The apparent amplitude of these action potentials was measured from the zero baseline on the voltage scale to the summit of the first negative peak. Since neural impulses were recorded as diphasic action potentials, MAP amplitudes referred to in Fig. 3 and this report were "relative" measurements of MAP amplitudes.

The duration of diphasic MAPs was taken as the interval under the first negative peak, measured from the rise of the action potential until it reached the zero baseline. From Fig. 3 it is clear that duration is a more sensitive index of irradiation damage than the MAP amplitude. With X-ray exposures greater than 6.4 kR, the duration of the MAP increased in a progressive fashion.

The pair of Ag-AgCl recording electrodes used to detect neural action potentials in this study were respectively 10 and 20 mm from the cathode. The interval between the cessation of the stimulus and the detection of the rise of

the action potential is referred to here as the detection period. The detection period includes the impulse conduction time between the cathode and the first recording electrode and the latent period of excitation. In Fig. 3 the detection period was altered after the nerve received 80 kR of X-rays. Changes in the detection period of the MAP gave indications of irradiation damage at exposures less than those required to alter the amplitude of the MAP.

In 16 experiments nerves were irradiated until excitability was completely inhibited. To fully block impulse propagation required from 293 to 304 kR with an average of 300 kR of X-rays. It was noted that the first 100 kR of X-rays in these 16 experiments did not alter the MAP amplitudes or MTS values. This finding is in opposition to the claim (8 to 11) that the onset of irradiation provokes a heightened MAP and a fall in the threshold.

Four of the 16 nerves irradiated exhibited only attenuation and ultimate suppression of neural activity. Twelve of the nerves irradiated produced a 4 to 10% increase in the MAP amplitude near 160 kR (average), which always occurred just prior to a rapid attenuation and loss of bioelectric activity (Fig. 3).

Increases in the duration of the MAP were initiated in 16 nerve preparations exposed to 20 kR of X-rays. In half of the experiments the duration of the MAP increased with only 10 kR of X-rays, while no alterations in the MAP amplitude was detectable.

Detection period changes in the MAP were provoked by 65 kR of X-rays in 9 of the 16 nerves irradiated to extinction. The other seven nerves required twice this X-ray exposure to introduce changes in the detection period. Four nerves affected by 65 kR of X-rays demonstrated a 4% decrease in the detection period before an increase was observed. Detection period changes induced by irradiation were apparent before X-ray induced MAP amplitude changes.

SUBMAXIMAL ACTION POTENTIALS

When the strength of a stimulus presented to a nerve was less than a MTS,

a submaximal action potential (SMAP) was generated. The voltage to evoke a SMAP defined a submaximal stimulus (SMS). In the material to be described, the SMS presented to nerves was not varied, or interrupted by a different strength stimulus. After a period of stabilization, the SMAP amplitude became constant. If a train of steady SMAPs was interrupted by a MAP, this intrusion tended to disturb the stability of the SMAP and another period was required to permit the nerve to again produce SMAPs of constant amplitude. To avoid this interference, MAPs were recorded only at the beginning and termination of each experiment. The irradiation process was started when there was sufficient evidence that the SMAP was steady.

In pilot studies 30 nerves with SMAPs ranging from 25 to 75% of the MAP were given 10 kR of X-rays. It was found that 15 nerves were insensitive to irradiation, four nerves demonstrated a decrease in the SMAP, and 11 nerves showed an increase in the SMAP.

In other experiments it was of interest to determine if changes occurring during the control period of stabilization were related to changes provoked by X-irradiation. The SMAPs of 36 nerves showed the following behavior under control conditions (no irradiation). The SMAP amplitude registered no variation in 14 nerves (S-type), 10 nerves (I-type) showed a spontaneous increase and 3 nerves (D-type) underwent a decrease in the SMAP amplitude. Nine nerve preparations (V-type) behaved like an I-type and later like a D-type nerve (or vice versa). V-type nerves were eliminated from this study. After 60 minutes, 27 control nerves obtained steady SMAP amplitudes, although the SMAPs of some D- and I-nerves became stable in 5 to 10 minutes (Fig. 4). A nerve was subjected to X-rays only when a steady SMAP persisted for 10 minutes.

The effects of 10 kR of 200 kV X-rays on the 27 nerves described can be readily summarized. The SMAP amplitude of 13 S-types nerves was not changed with irradiation (Fig. 5), but one S-type nerve showed a SMAP increase. Eight

I-type nerves increased their SMAP amplitudes during radiation treatment (Fig. 6); two I-type nerves had SMAP amplitudes which remained stable. Two D-type nerves had their SMAP amplitudes decline; the SMAP of one D-type nerve remained unchanged with 10 kR of X-rays.

In 7 experiments distinct from those just described it was noted that once 2 to 4 kR of X-rays initiated an alteration in the SMAP amplitude, the irradiation could be discontinued and the SMAP amplitude changes would continue until a new, steady amplitude was achieved.

These results did not support the position that irradiation in low doses only increased the SMAP, as claimed by others (5,17,22). Rather, ionizing radiation appeared to cause an interruption of the steady state condition of excitable nerve membranes. The unstable SMAP of an irradiated nerve approached stability along one route if it was a D-type nerve and along another route if it was an I-type nerve. Apparently, S-type nerves were more resistant to being made unstable with X-rays than D- and I-type nerves.

POLARITY REVERSAL OF STIMULATING ELECTRODES

Seymour and Dawson (20) claimed that reversal of the usual polarity of the stimulating electrodes completely neutralized the effects of X-rays on the SMAP amplitude.

In 4 experiments in which the anode was situated between the cathode and the recording electrodes, X-irradiation was capable of increasing the SMAP of I-type nerves (Fig. 7). SMAP amplitudes were heightened but it required about 8 kR of 200 kV X-rays to do so.

DISCUSSION

Nerve performs its function of impulse conduction in a high fidelity manner. Each impulse transmitted by nerve is a precise replica of the impulse that preceded it. It is, therefore, surprising that the initial bioelectric

response of nerve to irradiation is in doubt. Whether or not the amplitude of a conducted impulse is increased by low doses of ionizing radiation is still unresolved.

It was Bachofer (8) who made the original observation that the relative MAP amplitude of rat caudal nerve immediately increased with the administration of irradiation. Other reports (9 to 16.) employing rat caudal nerve and turtle's superior cervical ganglion also demonstrated that the relative MAP amplitudes were augmented by low doses of irradiation.

Allen and Nicholls (17) irradiated the phrenic nerve of the rat and could not find enhancement of MAP amplitudes. They repeated these experiments on the rat caudal nerve preparation Bachofer (8,9) and Bachofer and Gautereaux (10,11) had used and stated (17), "We have tried to confirm these results by imitating their experiments as closely as possible," but were unable to find increases in MAP amplitudes induced by X-irradiation.

The findings in this report are in disagreement with the assertion that relative MAP amplitudes are augmented by low doses of irradiation. MAPs were continuously monitored while frog sciatic nerves were exposed to 200 kV X-rays. In 19 trials the MAP amplitudes were unchanged by 10 kR of X-rays. In 16 other experiments the MAP amplitudes were unaltered even with 100 kV X-rays. This data is in harmony with other reports (1 to 8, 17 to 23) which failed to demonstrate irradiation enhancement on bioelectric activity.

Yamashita and Miyaska (21) exposed single nerve fibers from the sciatic nerve of the Japanese toad to beta irradiation and did not detect irradiation-enhancement of the action potential. When frog sciatic nerve was exposed to high energy deuterons and alpha particles (18), the summed action potential was not augmented. These data are in concert with the findings in the present report.

In some instances the relative MAP amplitudes, threshold to electric stimulation (sensitivity) and conduction velocity reported by Bachofer (9) and Bachofer and Gautereaux (11) using rat caudal nerve preparations were remarkably different 20 minutes before irradiation compared to the very start of irradiation. For example, graphs of Bachofer and Gautereaux (11) revealed that MAP amplitudes were 42% greater 20 minutes before irradiation than at the onset of irradiation, even though the stimulus strength applied to the nerve preparations was supramaximal. Hence, these caudal nerve preparations were depressed 42% below their optimal action potential amplitude at the initiation of irradiation. Despite this, these action potentials were identified as maximal action potentials (9,11). Irradiation augmented these neural potentials by 18%, but the action potential amplitudes failed to reach preirradiation, optimal values. Likewise, Bachofer (9) and Bachofer and Gautereaux (11) presented several graphs that indicated that conduction velocity and threshold for excitation (sensitivity) of rat caudal nerve were removed from their optimal values by 62% and 30% respectively at the onset of irradiation. In other reports by Bachofer (8) and Bachofer and Gautereaux (10) the bioelectric activity of rat caudal nerves was stable before irradiation. In discussing the MAP amplitudes from rat caudal nerve preparations employed in irradiation studies Allen and Nicholls (17) stated, "Furthermore, the caudal nerve is not very suitable for making such measurements, since although Bachofer and Gautereaux (11) state it is 'relatively unbranched' we have on one occasion counted 8 branches in 4 cm, with a corresponding reduction in the diameter by about 25% in 1 cm length."

Recently, Kaack (17) observed that not all frog sciatic nerves respond in the same way to beta irradiation. Some nerves from large frogs showed no irradiation enhancement of the MAP amplitude. When augmentation of the MAP amplitude occurred with beta irradiation, its initiation corresponded to an increase in oxygen consumption by the nerve. A second peak of oxygen consumption

occurred immediately before the MAP response exhibited rapid attenuation. In our work it was found that 12 sciatic nerves (out of 16) exposed to 200 kV of X-rays revealed a 4 to 10% increase in the MAP amplitude just prior to rapid attenuation. This small MAP amplitude increase may be related to the second oxygen consumption peak reported by Kaack (16).

If we direct our concern to reports dealing with the effects of irradiation on the SMAP amplitude of nerve, we find that the information is ambiguous. Some authors (20,22,24,25) present evidence to support the view that the SMAP amplitude is heightened by irradiation, while other investigators (17,26,27) possess results which oppose this position. Seymour and Dawson (20) found that 100 R of 50 kV X-rays always heightened the SMAP amplitude of frog sciatic nerve, and they maintained that the SMAP increase proceeded from zero dose. In their work (20) SMAPs were generated about one per 5 sec and each SMAP was followed by a MAP. In this present study it was our observation that a SMAP-MAP-SMAP routine of recording created unstable SMAPs in most nerve preparations and should be avoided.

In 57 experiments frog sciatic nerves were exposed to 10 kR of 200 kV X-rays. It was found that the SMAP amplitude of 31 nerves (54.4%) remained unchanged, while 20 nerves (35.1%) increased and 6 nerves (10.5%) decreased with irradiation. Allen and Nicholls (17) observed a similar variability while studying the influence of X-rays on the SMAP amplitudes of rat phrenic nerves. In their work (17) 9 phrenic nerves were irradiated; the SMAP amplitude was unchanged in 2 nerves, increased in 5 nerves, and decreased in 2 nerves. Our findings and Allen and Nicholls (17) report do not support the claim of Seymour and Dawson (20) that irradiation only heightens the SMAP amplitude.

It was our observation that the SMAP amplitude responses provoked by irradiation tended to follow the SMAP amplitude pattern in the preirradiation interval. Thus, nerves (S-type) with SMAP amplitudes that remained stable

throughout the control period for the most part were insensitive to 10 kR of X-rays. Nerves with SMAP amplitudes that increased (I-type) and nerves with SMAPs that decreased (D-type) in the initial portion of the control period, tended to exhibit similar behavior with irradiation.

It is possible that SMAP amplitude behavior of D- and I-type nerves is a consequence of the excitability changes in the different phases of the after-potential of impulses. During the negative afterpotential (supernormal period), frog sciatic fibers have been reported to be more easily excited (30 to 32); throughout the positive afterpotential (subnormal period) excitability was depressed below resting threshold (33).

Since the physiologic basis of temporal instability of SMAP amplitudes is not known, we are left with speculation. It appears relevant that interactions between fibers have been demonstrated for crayfish axons by Katz and Schmitt (34). They showed that a non-active nerve could be made active by having the negativity from an impulse in an adjacent fiber coincide with the arrival of an electric subthreshold stimulus to the nerve not previously excited. There does not appear to be any evidence from cable theory that would prohibit such an occurrence in a myelinated nerve.

The data in this report does not support the contention that irradiation must increase the SMAP amplitude. In general, irradiation was associated with no change in the SMAP amplitude of S-type nerves, increases in the SMAP amplitude of I-type nerves and decreases in D-type nerves. It was reasonable to interpret these results to mean that X-rays caused an interruption of the steady state condition of I- and D-type nerves. The attempt of neural membranes to return to a steady state was reflected by the nerve-type being irradiated.

The following observations lend credence to this interpretation. First, when irradiation provoked changes in SMAP amplitudes, these changes were of limited magnitude. That is, the SMAP became stable after a finite dose of

continuous irradiation and further X-irradiation was no longer effective in altering the SMAP. Secondly, once irradiation initiated a SMAP amplitude change, the irradiation process could be terminated and SMAP amplitude alterations would continue until a new steady SMAP was achieved.

The basic reason for the variation in the electric response of neural membranes to low doses (below 100 kR)of X-rays, remains unknown. Sodium ion permeability in nerve increases by a factor of 500 in going from the resting to the active state (35). It could be proposed that irradiation further increases sodium ion permeability. This would account for the increase in the MAP amplitude at the onset of irradiation (9 to 16). It would follow that in similar experiments in which no alteration in the MAP amplitude occurred (1 to 8, 17 to 23), irradiation failed to alter sodium ion permeability. To assign such a conflicting role to sodium ion permeability is not attractive.

Tissue culture studies have indicated that glial cells (36) and Schwann cells (37),associated with neurons, are more sensitive to irradiation than nerve cells. Unmylinated axons of dorsal root ganglia were denuded of investing Schwann cells by X-irradiation (37). Since peripheral nerve fibers are covered by a layer of connective tissue (endoneural cell sheath) and an outer covering of Schwann cells (neurolemma cell sheath), it is possible that some of the changes in bioelectric activity of irradiated nerve fibers is due to variations in the physiologic state of these satellite cells.

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LEGENDS

Fig. 1 Maximal action potentials recorded from an isolated frog sciatic nerve. On each oscillogram was superimposed the exposure (in R units) of X-rays accumulated by the nerve. Negativity for the nerve surface was upward in all oscillograms in this report.

Fig. 2 Maximal action potentials obtained from the same nerve which produced Fig. 1. The exposure (in kR units) of X-rays delivered to the nerve was superimposed on each oscillogram.

Fig. 3 Relative values of amplitude, duration, and detection period of the maximal action potential plotted as a function of the X-ray exposure (kR units) delivered to an isolated sciatic nerve. The action potentials of Figs. 1 and 2 provided the information for the construction of this diagram. The amplitude of the action potential was plotted as a percent of the initial (zero kR) maximal action potential, which was defined as 100%. Duration and detection period were plotted as percent changes from the zero kR value.

Fig. 4 Submaximal action potentials (SMAPs) obtained from an isolated nerve (S-type) during the period of stabilization prior to irradiation. The SMAP amplitude of this nerve preparation became stable in 6 minutes at a value 65% of the maximal action potential (10.5 mV).

Fig. 5 Submaximal action potentials (SMAPs) recorded from isolated sciatic nerve (S-type) exposed to 200 kV X-rays. The control SMAP (marked 0) was 47.5% of the nonirradiated maximal action potential (marked MAP, 0 R). Irradiation did not alter the SMAP amplitude of this nerve. The exposure (in R units) of X-rays delivered to the nerve was superimposed on each oscillogram.

Fig. 6 Submaximal action potentials (SMAPs) obtained from a sciatic nerve (I-type) subjected to X-rays. The control SMAP (marked SMAP 0) was 32.5% of the nonirradiated maximal action potential (marked MAP 0 kR). Irradiation of this nerve provoked an increase in the SMAP amplitude. The exposure notation was in kR units.

Fig. 7 Action potentials generated with a sign reversal of the conventional stimulation procedure. Here anodal stimulation has been employed as evidenced by the downward deflection of the shock artifact. Submaximal action potentials (SMAPs) were recorded from a sciatic nerve. The control SMAP (marked SMAP 0) was 60% of the nonirradiated maximal action potential (marked 0 kR). X-rays administered to this nerve provoked an increase in the SMAP amplitude. The exposure notation was in kR units.

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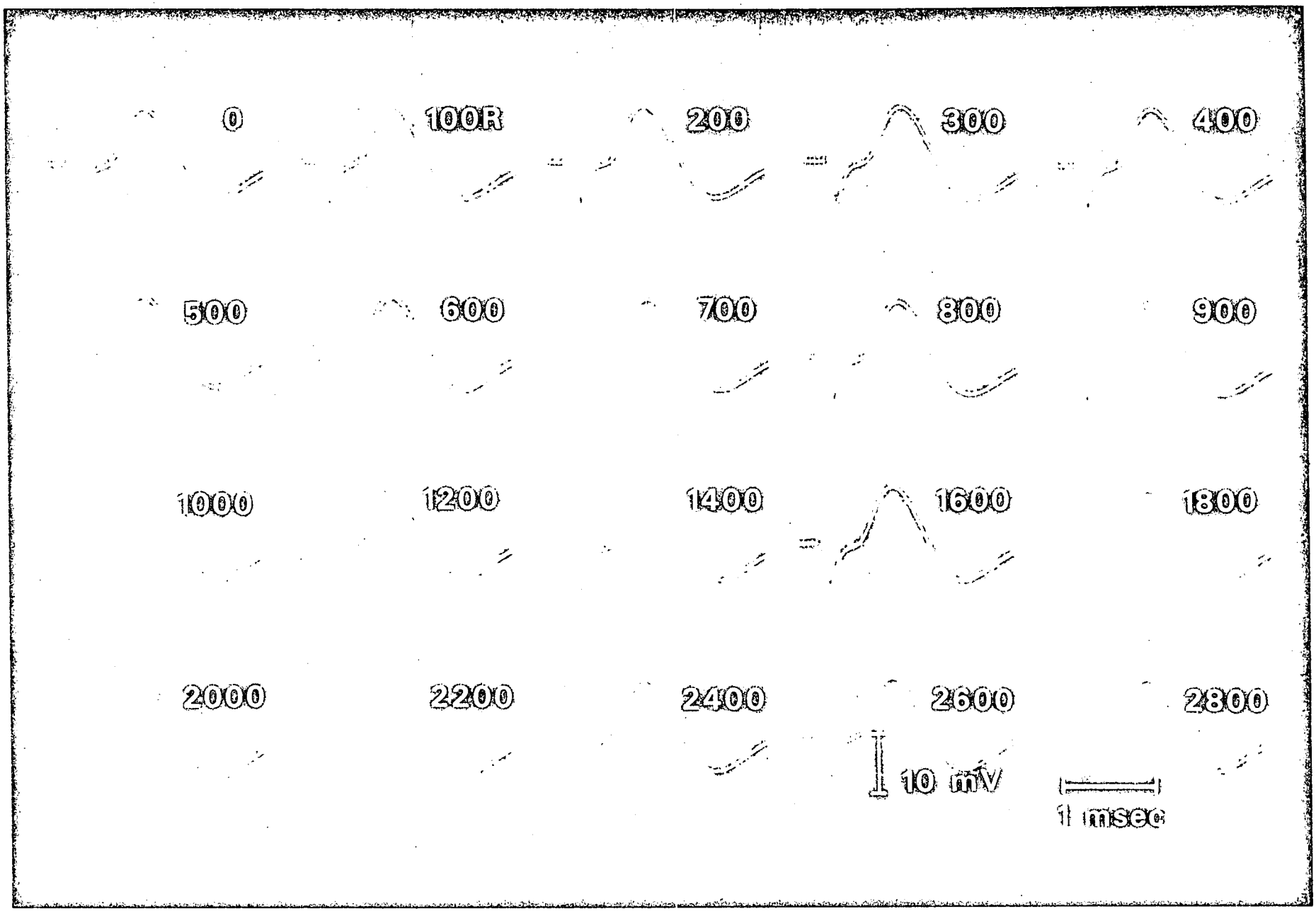
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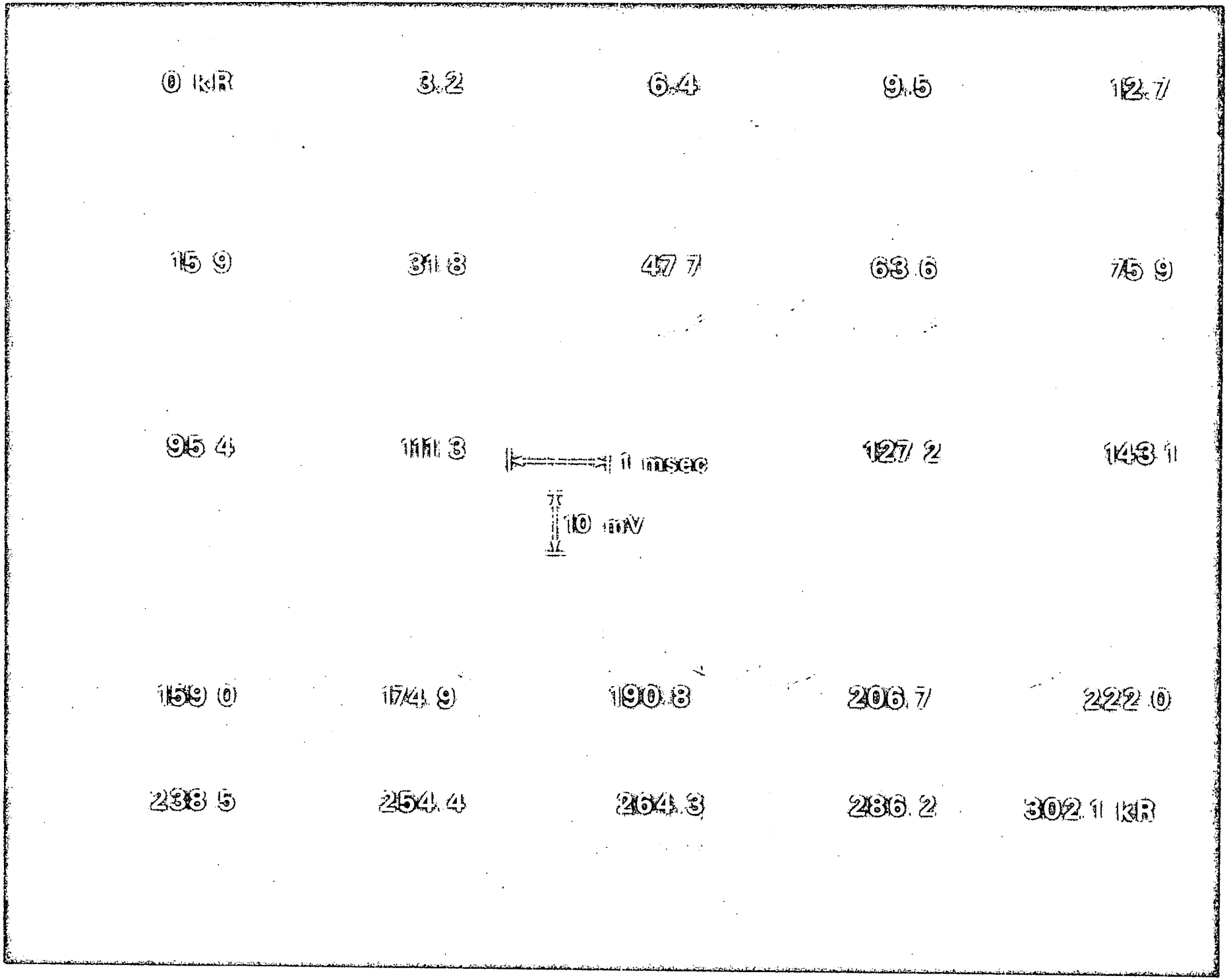
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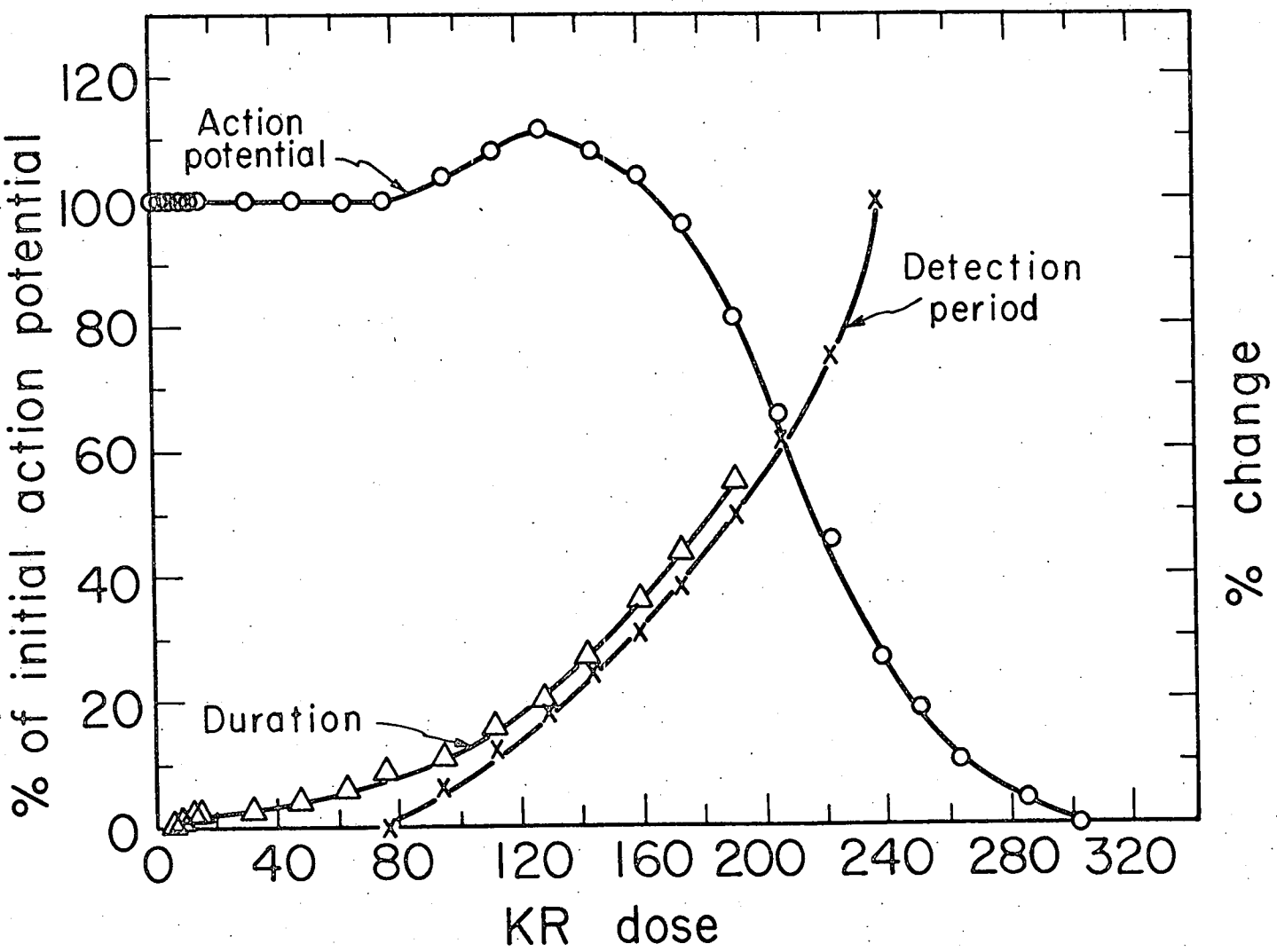

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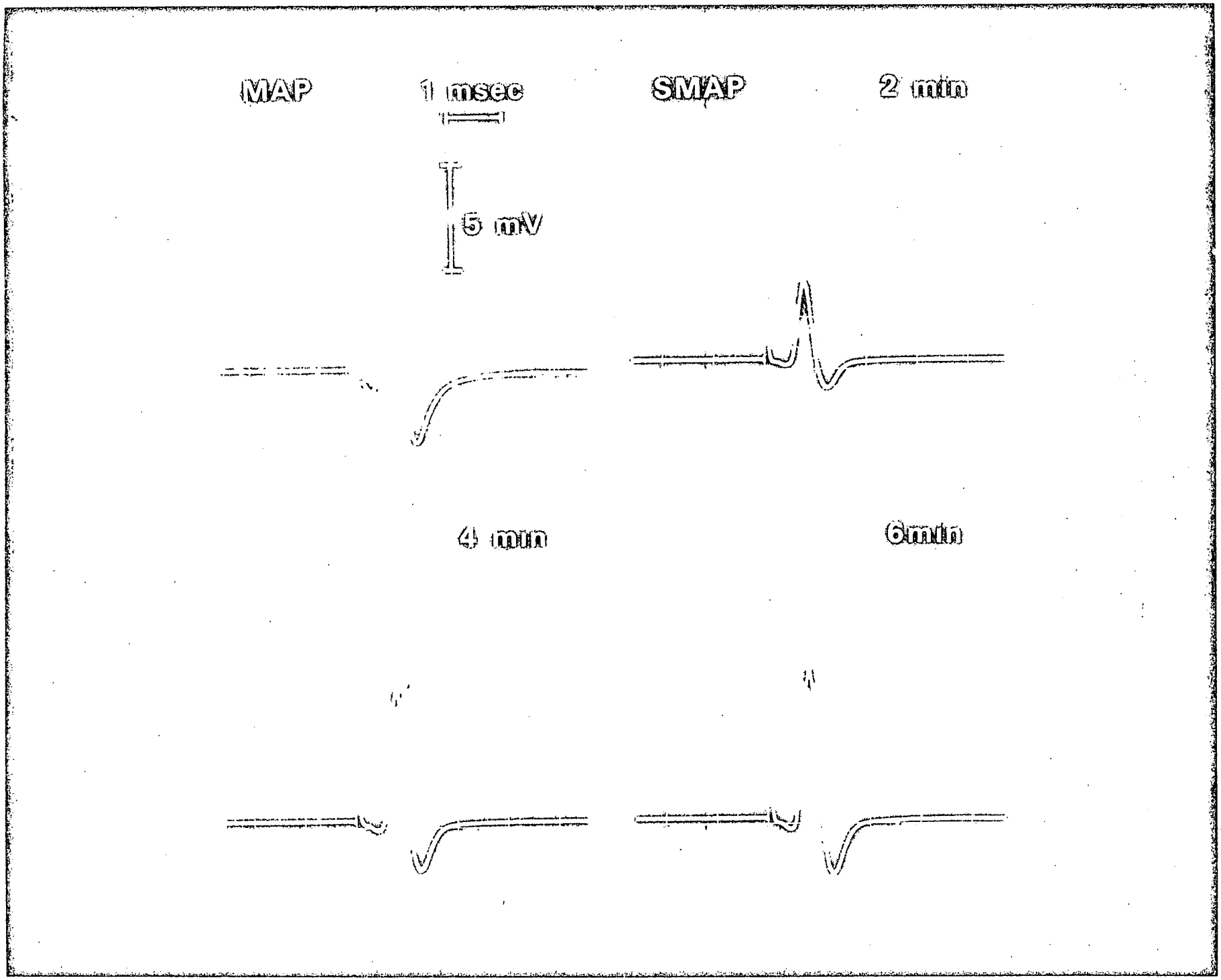
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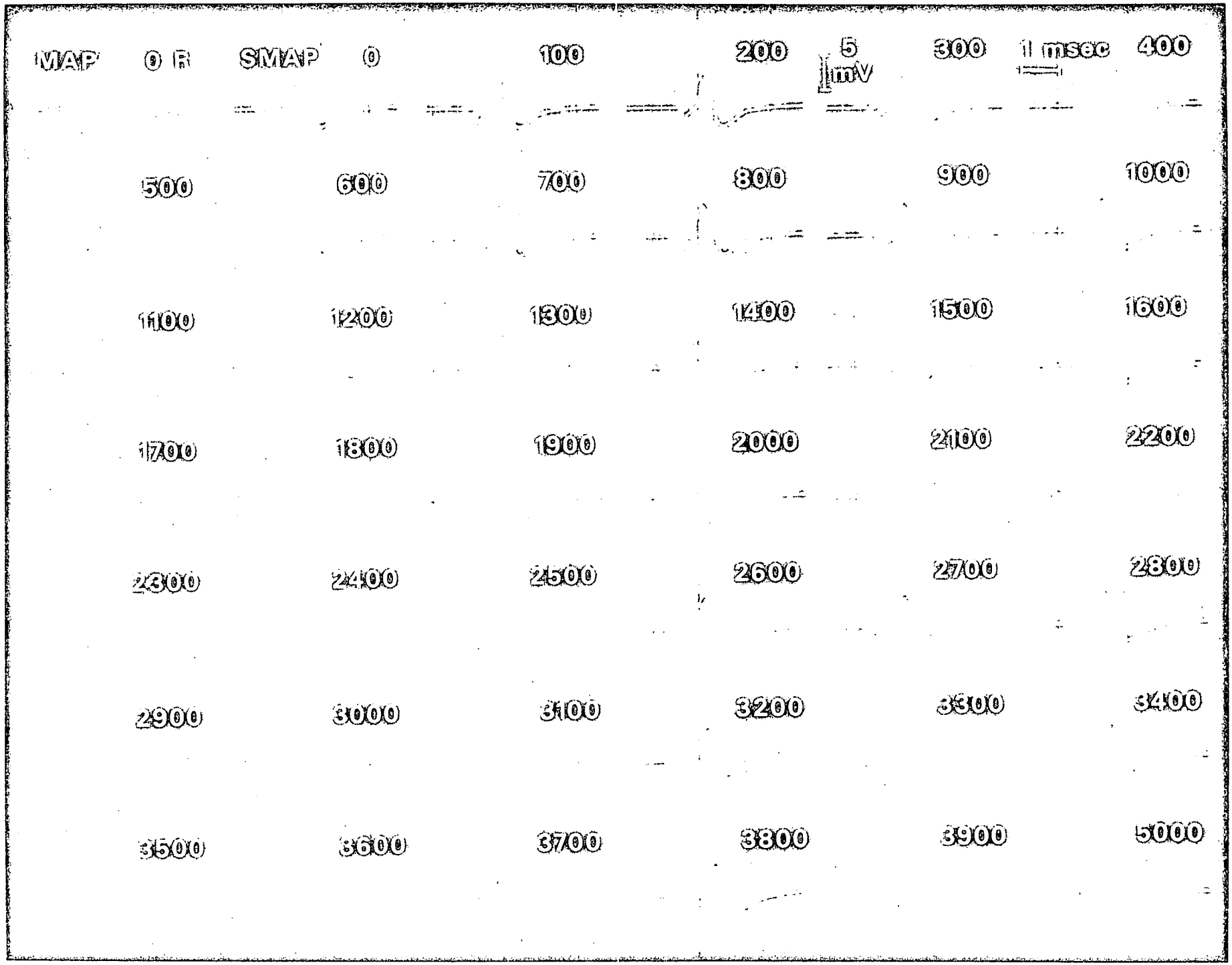
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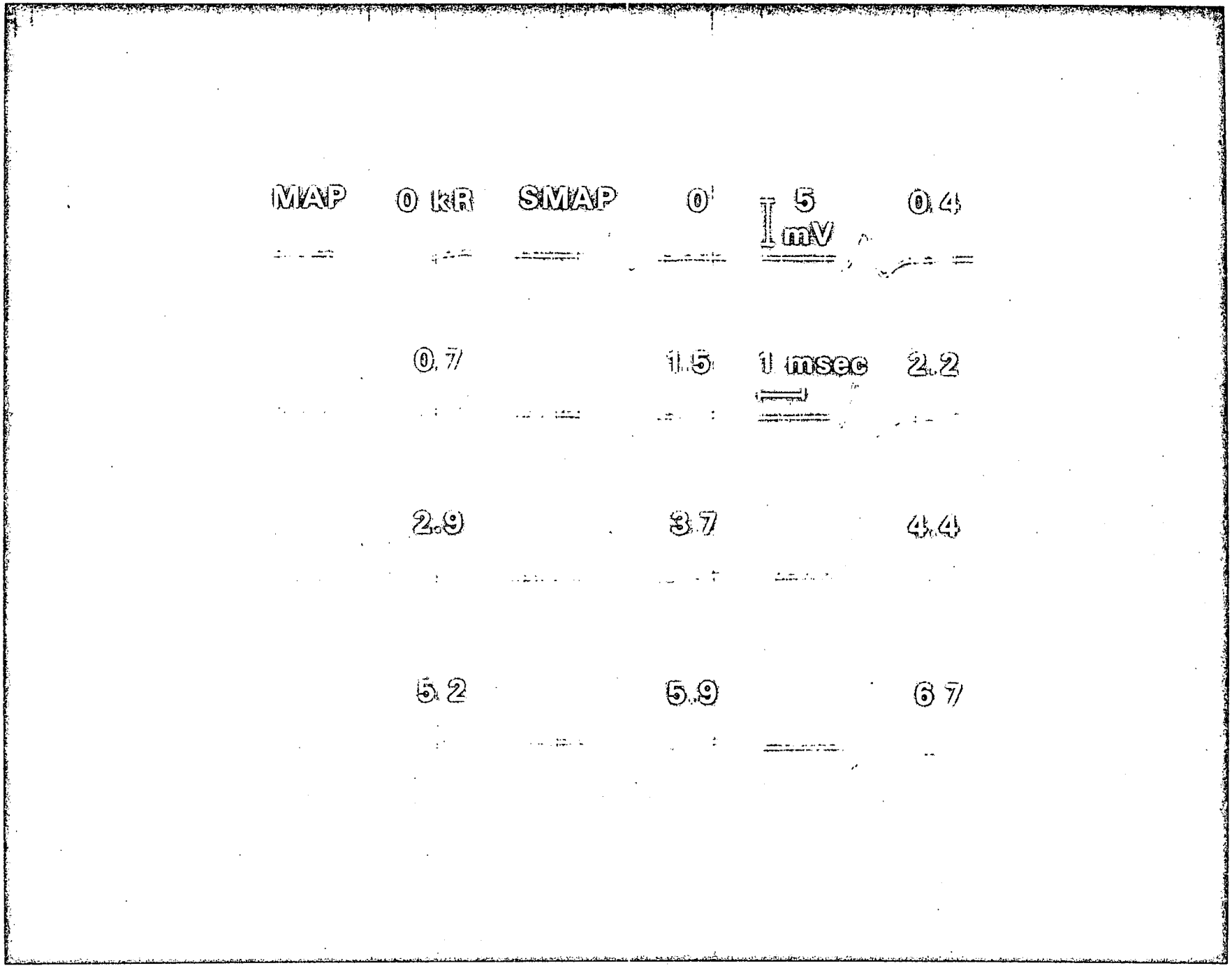
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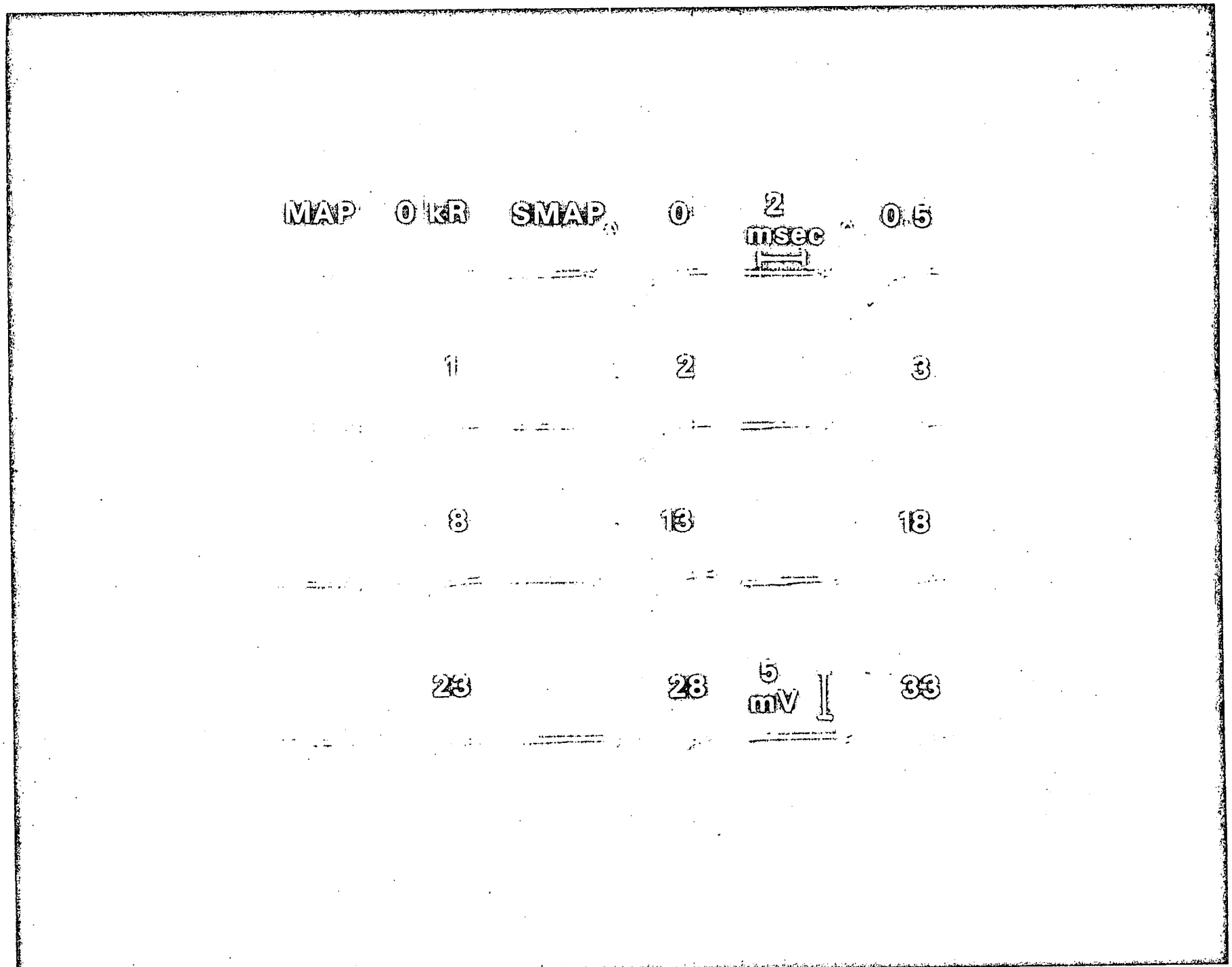
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