Bioelectrochemistry and Bioenergetics **2**, 13–25 (1975)

Electrical Stimulation of the Nervous System: The Principle of Safe Charge Injection with Noble Metal Electrodes *

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Summary

Electrical stimulation of the nervous system is of increasing importance for a variety of prospective prostheses. Many of these involve direct chronic stimulation of the cerebral cortex. The electrochemical reactions which may occur at the Pt or other noble metal|physiological saline interface were discussed. A variety of undesirable reactions may occur, *viz*, the electrolysis of water, the oxidation of the saline, the dissolution of the metal, and the oxidation–reduction of organic materials. There are two highly desirable methods of injecting charge from a noble metal into tissue: these involve modification of the electrical double layer at the interface, or capacitive coupling *via* symmetrical surface–layer oxidation–reduction processes.

Two principles of tissue stimulation for electrochemically completely safe conditions are proposed:

1. Perfect symmetry of the electrochemical processes in the two half–waves of the pulses should be sought. This implies that we do not generate any electrolysis products in solution. One approach to achieve this would appear to involve use of perfectly charge–balanced waveforms of controlled magnitude.

2. The aim should be to inject charge *via* non–faradaic or surface–faradaic processes, to avoid injecting any possibly toxic materials into the body.

The experiments required to specify the amounts of charge which may be injected *via* these latter processes are described.

Considerations affecting alternative choices to the use of Pt for microstimulation electrodes are discussed.

Introduction

The interaction of electricity with the human body has been known since the days of GALVANI and VOLTA. Increasing in modern times there has been great interest in the possible use of a variety of prostheses

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* Presented, but not discussed, at the 2nd International Symposium on Bioelectrochemistry, Pont à Mousson, 1–5 Oct. 1973.

involving chronic electrical stimulation. For example. BRINDLEY and LEWIN [1] described a prototype visual prosthesis involving implantation of an electrode array onto the surface of the visual cortex of a blind patient. By means of appropriate pulses, the patient was caused to experience sensations of light (phosphenes). This preliminary report has been the starting point for an extensive feasibility investigation sponsored by the National Institute of Neurological Diseases and Stroke of the National Institutes of Health, and is the focus of our present work.

This prospective prosthesis is only one of a very broad range of prostheses using implanted electrodes being investigated: for example SHEALY and others [2-7] have described an implanted dorsal column electroanalgesic device. Also, there have been a number of efforts to use electrical neuromuscular stimulation to treat paraplegia and hemiplegia. [8-24] In other efforts, an attempt has been made to construct an auditory prosthesis involving implanted electrodes [25] and BOBECHKO [26] describes the possible treatment of scoliosis by means of an implanted electrode. We may note too the peroneal stimulator of the Ljubljana group to help correct footdrop. [27-30] They have investigated both surface and implanted electrodes. PINNEO *et al.*[31] have explored the possible use of an implanted electrode device in the brain as a motor prosthesis for stroke patients.

All of these prostheses will involve applying chronic electrical stimulation to the nervous system, in some cases directly to the cerebral cortex. Quite stringent electrochemical sequences must be used for this stimulation. For example, in the device of BRINDLEY and LEWIN [1] Pt electrodes with an area of $\sim 6 \times 10^{-3}$ cm^2 needed to be pulsed for 0.4 ms with $\sim$3 mA (estimated from their data) at 30 Hz to produce a phosphene. This is equivalent to a current density of $\sim$500 mA/cm^2 during the pulses whilst admitting a charge of $\sim$200 μC/cm^2. The electrochemistry involved in injection of such impulses to the body has not been investigated in any detail and that is the purpose of the present series of papers.

In this paper, we will review what is expected about the behavior of Pt (and by implication other noble metal) electrodes under transient conditions in physiological saline, and we will indicate some of the problems which may be encountered in their use in the above prostheses. A principle for totally safe charge injection with Pt and other noble metal electrodes will be developed, and a description of the experiments required to apply this principle in practice will be presented. In further papers, which we shall publish shortly, we will try to define experimentally the safe limit of charge which can be injected into the nervous system with Pt electrodes. Then, since as we show below, the "real area" of the Pt electrode is the crucial quantity needed to define the safe limit for charge injection, we will describe how to measure it *in vivo*. In a further application of these procedures, we will present data on the injection of charge from stable, high surface area Pt microelectrodes. Here the aim is to improve spatial resolution in the prosthesis by using a very small electrode, and to inject charge safely with it by limiting the "real" current and charge densities.

Electrochemical processes which can occur during stimulation; principle of safe charge injection

Typical stimulation parameters involve injecting 1–4 mA with an electrode of area 0.005 to 0.01 cm^2 and pulse durations of 500–1000 μs at repetition rates of ~10–100 Hz. These charge injection requirements can involve a variety of possible electrochemical reactions which previously have not been investigated in much detail. A number of possible electrodes have been considered for chronic stimulation, *e.g.*, Pt, W, and stainless steel. [32,33] To date Pt has been one of the more satisfactory materials, rarely showing any macroscopic changes, and frequently being useful without causing obvious lesions.

There have been some investigations of the safety and effectiveness of various stimulus waveforms. Is is well known that repeated application of constant polarity pulses leads to formation of lesions. [34,35] To lessen these effects, LILLY and co–workers [36–38] have worked with symmetrical current waveforms (so–called " balanced–biphasic ") which they found mitigate the probability of lesion formation. They place great emphasis on short balanced pulses. HESS [40] claims that the length of the biphasic pulse is not critical in determining lesion formation. MILLER *et al.* [39] showed that there is no practical difference in sensitivity to lesions between a LILLY weveform and stimulation with 60 Hz sine waves. These caveats notwithstanding, it is clear that biphasic stimulation is preferable to monophasic stimulation.

There have been a number of electrical engineering–type studies of electrodes aimed at determining their impedance. [41–46,49,89–92] For example, WEINMAN and MAHLER [41] investigated the behavior of stainless steel, W and Pt. The equivalent circuit of the electrode was represented by an *RC* network, a method pioneered by DOLIN and ERSHLER. [47] WEINMAN and MAHLER used repeated pulses, and did not concern themselves with the state of the electrode's surface before starting. They noted pulse–width dependence of the impedance behavior of Pt. In a later paper, [42] WEINMAN emphasized the need to specify the current, the electrode voltage drop, and the pulse duration to understand the processes at a stimulation electrode. He disputed LILLY *et al.*'s conclusions [36] that stimulation with a symmetrical biphasic waveform leads to symmetrical electrochemical reactions at the electrode tip since, although one may put equal charges in the half waves of the pulse, the voltage transients in the two wave–halves are seen to be quite different. To our mind this conclusion of WEINMAN shows the errors which a purely mechanical use of "electrical equivalents" can lead to, if the underlying electrochemistry is ignored. This point will be taken up further below when we discuss the transient electrochemical processes which can occur at the Pt | solution interface. In this connection, it is important to realize also that the actual impedance data, themselves, are not likely to be of sufficient generality for practical purposes.

MANSFIELD [43] studied electrochemistry of the electrode | heart tissue interface. Again, the approach was substantially an electrical impedance

investigation. He recommends the use of constant current rather than constant voltage pulses as the access resistance loss is constant and more easily calculated in the former case *. MANSFIELD makes considerable point of the fact that a good deal of the applied energy is dissipated in electrode polarization, as do GREATBATCH *et al.* [44,45] The latter studied the polarization characteristics of Ag, Au, Pt, Pt–10% Ir, orthodontic Au, 304 stainless steel and elgiloy, with emphasis on their use in cardiac pacemakers. They showed that under the conditions where these electrodes were used, some of them discolored and gassed. SCHWAN [46] also investigated the *a.c.* impedance of Pt electrodes. Like WEINMAN, he emphasized the electrical properties of the system and tended to disregard the underlying electrochemical process. His results must be used with caution since he applied ~3.5 mC/cm² to the electrode in each pulse. The discussion below shows that this is at least 5 times the maximum permissible charge per cycle even to avoid water electrolysis. In a later paper, SCHWAN claimed that the maximum safe stimulation current density permissible is 1 mA/cm² [86]; it appears that this view is developed with respect to heating effects with macro-electrodes. [87] In our view, the electrochemical emphasis should be on maximum charge density rather than on current density.

We will now review what is known about the electrochemistry of the Pt|saline interface and try to emphasize the uncertainties which must be resolved. The electrochemically significant components of tissue fluids are water (~55 *M*), NaCl (~0.13 *M*), HCO_3^- (~0.02 *M*), CO_2 (~0.05 atm) and various organic materials such as glucose (1.2–2.4 m*M*) and proteins (200–400 mg/l). The following is a summary of the reactions which can occur when Pt is made a *d.c.* anode in this solution :

Electrolysis of water : $2\,H_2O \rightarrow O_2\uparrow + 4\,H^+ + 4\,e^-$ (1)

Oxidation of saline : *e.g.* $Cl^- + H_2O \rightarrow ClO^- + 2\,H^+ + 2\,e^-$ (2)

Oxidation of metal : *e.g.*, $Pt + 4\,Cl^- \rightarrow PtCl_4^{2-} + 2\,e^-$ (3)

Oxidation of organics: *e.g.*, $C_6H_{12}O_6 + 6\,H_2O \rightarrow 6\,CO_2 + 24\,H^+ + 24\,e^-$ (4)

Of these, reaction (1), the electrolysis of water, is harmful because it produces gas and because there is a local pH change near the electrode. The latter can generally be tolerated, at least under the transient conditions of most normal stimulation procedures, but gas evolution is very damaging. Reaction (2), which is only representative of the possible

* There is another reason why controlled current, rather than controlled voltage pulses, should be used in stimulation, if charge-balanced wave-forms are required: the surface reaction impedances are different in the anodic and cathodic direction ; hence, charge-balance can only be achieved with controlled current pulses.

saline oxidation processes, but which is the most likely, would probably be harmful because ClO^- is a very strong oxidizing agent and it is kinetically active. Some other possible saline oxidation products, such as ClO_4^-, are also strong oxidizing agents but less kinetically active. The major concern with producing these would be fear of their possible specific physiological toxicity. A further possibility, which is of great relevance in Cl^- – containing media, is the oxidation and dissolution of the noble metal itself, *e.g.*, reaction (3). In this instance, the physiological activity of the main dissolution product has been demonstrated. [50] Pt dissolution products are in any case powerful oxidizing agents, which can be reduced by organic species present in the medium, *e.g.*, by glucose. The dissolution of Pt under anodic conditions in Cl^- – containing media is well-known [51] and is certainly a factor of immense relevance. A final possibility, shown for example in the case of glucose [reaction (4)], involves the oxidation of organics. Glucose can be partially oxidized (*e.g.*, to gluconic acid), or all the way to CO^2. These kinds of processes pose non special problem provided that sensitive tissue is not itself attacked and provided also that the oxidation products are not themselves toxic.

The above processes should not be permitted to take place under chronic stimulation conditions. If they do occur, their effects may be minimized by use of balanced waveforms which have no net direct current component, *e.g.*, those of LILLY [36-38] and HUNSPERGER. [52] This kind of waveform certainly has its major impact in preventing reaction (1) from proceeding ever more damagingly in each successive monophasic pulse. If such a waveform also minimizes reactions (2)–(4), it is fortuitous, since the electrochemistry of the charge injection processes appears not to have been investigated earlier in any detail.

There are three possible processes available for charge injection into the nervous system with a noble metal (Pt) electrode which may be regarded as substantially safe. These are double layer charging, surface oxidation, and H–atom plating:

Double layer charging: $Pt(—)$ repels $Cl^- \rightleftarrows Pt(+)$ attracts Cl^- (5)

Surface oxidation: *e.g.*, $Pt + H_2O \rightleftarrows Pt + 2\,H^+ + 2e^-$ (6)

H–atom plating: $Pt — H \rightleftarrows Pt + H^+ + e^-$ (7)

Here the double layer process involves the attraction and repulsion of ions from the bulk of the solution to the vicinity of the metal. No chemical change takes place, just a redistribution of the ions in the so–called "double layer" near the metal. This process is reversible and acts very much like an electrical capacitor. A second possibility, which does involve chemical change but still is attractive in principle, is reaction (6), the chemically–reversible surface oxidation and reduction of the electrode. The H–atom plating process is an extremely attractive possibility. Thus, it occurs at low potentials, which minimizes possible

metal dissolution, and it is kinetically very reversible and therefore consumes little of the applied energy.

The relation of these charge injection processes may be seen in Figs. 1 *a* and 1 *b*, which represent anodic charging curves for a smooth Pt electrode in a strong acid solution. As it ls well known, we can distinguish four primary potential regions [53]: A from about the hydrogen potential to about 0.35 V, the hydrogen surface layer oxidation region; B from ~0.35 to ~0.85 V, the double layer charging region; C from ~0.85 V to ~1.8 V, the surface oxidation region; D the O_2–evolution region. In regions A, B and C, we can respectively inject ~250, ~25,

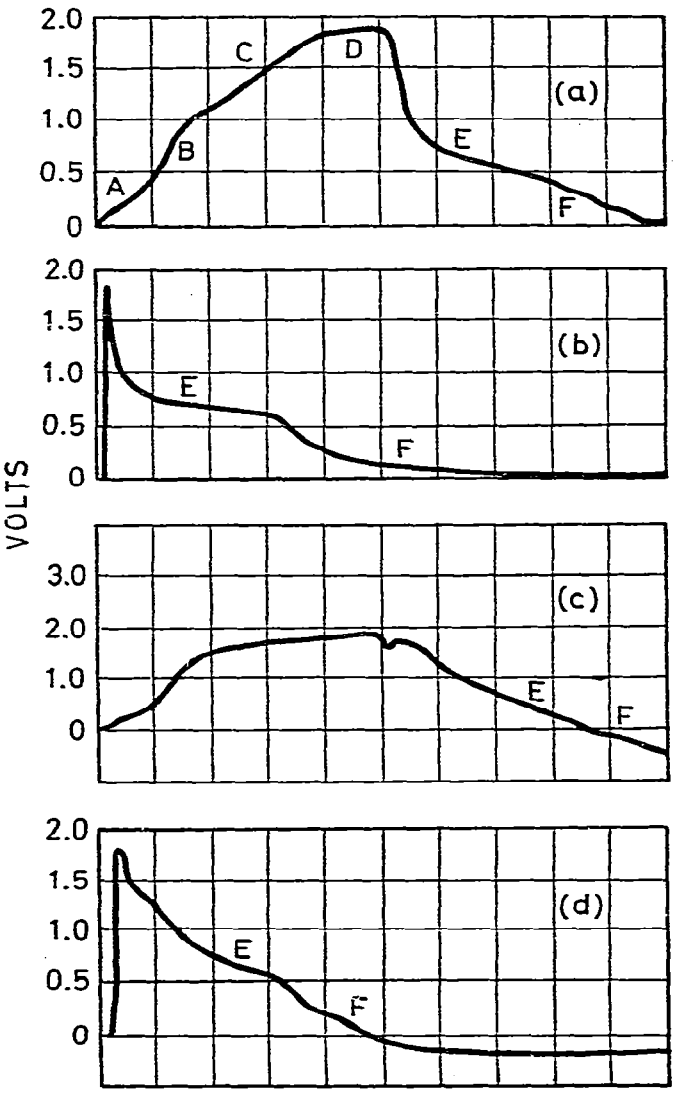

Fig. 1.
Anodic charging curves at 100 mA/real cm² in 1 *N* $HClO_4$ [(a) and (b)] and 0.13 *M* NaCl buffered at pH 7.3 with HCO_3^-–CO_2 [(c) and (d)].
Figs. (a) and (c) show current reversal at 100 mA/real cm², as might be used in a LILLY waveform. Figs. (b) and (d) show current reversals at 1 mA/real cm², to show regions E and F in more detail. Potentials are shown against the reversible hydrogen electrode in the studied solution. Each abscissa square is equivalent to 200 μC/real cm².

and 450–500 μC/real cm² * of charge. Also shown in Fig. 1 are current reversals taken to sample the oxidation processes which have occurred during the previous anodic pulse; we may distinguish the oxide reduction region, E, and the H–atom plating region, F.

The asymmetry of the voltage waveform in the two directions is to be noted but, contrary WEINMAN'S view, [42] *the symmetry of the chemical processes* is emphasized. To a first order, processes A, B and C between them would allow us to inject up to ~750 μC/real cm² (depending somewhat on the current density) before any process of the kind of reactions (1)–(4) occurs. Reactions (5) to (7) allow us to interact essentially capacitively with the nervous system *without transforming any solution chemicals* (other than small changes in *local pH, which the body's* buffering system should be able to take care of). It is quite clear that *the maximum charge which can be admitted via these processes is a very conservative estimate of the maximum safe stimulation charge.*

The situation in Cl^- – containing media, and in physiological saline in particular, is much less well understood. Three points are very well established: Cl^- strongly adsorbs on the Pt surface and inhibits both transient and steady–state oxide formation [55-61,70,71]; Pt can dissolve, particularly in acid solution, usually to $[PtCl_6]^{4-}$. [61,65] (WETZEL *et al.*[88] note possible Pt dissolution during stimulation; HENCH *et al.* [48] prove it). Suppression, *i.e.*, passivation, of both Cl_2–evolution (in acid solutions, this is the main product of Cl^- oxidation) and Pt dissolution appears to be associated with film formation, [66] although whether this film is an oxide [67] or a chloride or oxychloride [62,68,69] is in dispute.

To our knowledge, there have been only two papers on the properties of Pt under transient–oxidative conditions in neutral chloride solutions: PETERS and LINGANE [68] postulated the formation of platinum chloride and oxychloride films, which were very stable; they worked only with μA/cm² charging rates though. PIERSMA *et al.* [72] investigated the behavior of the electrode under quite rapid transient circumstances, mostly in more acid environments. Their results allow no conclusions of relevance to the present problem except to note that Cl^- does not affect the amount of adsorbed hydrogen.

The kinds of charging curves, which we have observed in physiological saline, are shown in Figs. 1 (c and d). These are quite distincly different in shape from those obtained in strong acid solutions and they do not allow the clean separation of the surface processes, which is possible in the latter case.

We may note, as it has been pointed out, [73] that Pt does dissolve a little during the formation and removal of its oxide even in non–Cl^- – containing media. It may well be queried then as to whether, considering that all the damaging reactions shown, *i.e.*, reactions (1)–(4),

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* The definition of "real area" of Pt electrode is discussed in our earlier paper. (54) The *in vivo* determination of real area will be described in a later publication. Typically, a bright Pt electrode has a roughness factor of 1.3–1.5.

are oxidation reactions, we should use the Pt electrode in stimulation as an anode or as a cathode during the first half cycle. The possible reason for using it as an anode is because of the influence of organic materials present in the body. All of our previous work with Pt electrodes [74-79] indicates that these compounds will adsorb strongly onto the surface of the electrode when it is at rest. If the electrode is used as an anode, these adsorbed materials will act as an additional buffer against reactions of the type (1)–(3) because they tend to be oxidizable. On the other hand, the adsorbed organic materials are most frequently not reducible, and they block the surface in the cathodic direction for the normal reaction, H–atom deposition on the surface, *i.e.*, region F of Figs. 1 (a and b). Hence the evolution of H_2 from water, a potentially very damaging process, occcurs with less charge injection than on a clean surface. *

This line of reasoning is less persuasive under the multiple pulse conditions frequently used in stimulation since the electrode will probably be kept organic–free by the successive pulses. Under these conditions, the choice between leading with the anodic or cathodic pulses may well hinge on whether we prefer a transient acidity followed by neutrality or a transient alkalinity followed by neutrality. Only experiment can answer this question.

In summary, we may state the following as principles of a tissue stimulation procedure which is electrochemically completely safe :

1. Perfect symmetry of the electrochemical processes in the two half–waves of the pulses should be sought. This implies that we do not generate any solution electrolysis products, since they will not be totally recaptured during the second half–cycle. One approach to achieve this would appear to involve use of perfectly charge–balanced waveforms of controlled magnitude.

2. The aim should be to inject charge *via* non–faradaic or surface–faradaic processes, to avoid injecting any possibly–toxic materials into the body.

Information needed to specify safe stimulation procedures

It is clear that double layer charging, the surface oxidation, and the H–atom plating processes, reactions (5)–(7), are the preferred modes of charge injection from a noble metal stimulation electrode to the nervous system, since they are reversible and involve containment of all possibly noxious products on the surface. The major question we must

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* There are many indications in the literature that the response of a Pt electrode is notably different during the first few pulses of a train (*e.g.*, Ref. 88). In our view, this most likely results from these adsorbed organic materials.

answer is "*how much charge can be injected via these processes* in each pulse *without producing any solution product?*" In trying to answer this question, we have used reverse chronopotentiometry, solution chemical analysis, and the rotating ring and disk electrode. The objective in all cases has been to apply a suitable anodic stimulation pulse and to attempt to analyze for the amounts of electrolysis product which escape into the solution.

Since useful tissue stimulation will involve a chronically-stimulated electrode, the answer to this question must be known with a very high degree of precision. Correspondingly, very sensitive integration and signal-to-noise enhancement techniques must be used: in one experiment, the electrode is cycled in physiological saline, using the biphasic stimulation pulse under test, and is examined for increase of surface roughness using the techniques (and area-measurement solution) of Figs. 1 (a and b). The thesis is that Pt entering the solution will result in an increase of the surface roughness. Another procedure involves employing a Pt disk with an Au ring and holding the potential of the Au ring so as to accumulate any (small) amounts of Pt which might go into solution during a stimulation pulse at the Pt disk. This Pt, accumulated on the Au ring after many cycles at the disk, is then analyzed by surface-chemical or electrochemical study of the ring. Experiments along these lines are in progress for the Pt electrode and will be reported in later papers in this series.

Finally, as the above discussion makes clear, it will in many cases be necessary to measure the real area of the electrode *in vivo*. Techniques to do this will also be ported later.

Possible alternatives to Pt

The intrinsic factors which will decide the choice among the different noble metals in physiological saline will relate to the relative stability of the chloride complexes, by means of which the metals dissolve, and of the passivating layers (oxides?) which may protect them. Judging from the reversible potentials for the formation of the major chloride complexes,[80] we might assert an order: Au better than Ir>Pt>Rh. Based on similar data for ease of bulk oxide formation, we might assert a preferred order of: Rh>Ir>Pt>Au. This list is only the most preliminary guide, since the actual passivating film under transient conditions is only tenuously related to the bulk oxides of the metal, and some specific experimental investigation of the various noble metal alternative must be undertaken.

Another possibility of some interest is the RuO_2 electrode, the so-called "dimensionally stabilized anode" of the Cl_2-cell.[84] It appears that the surface capacity of the oxide's partial reduction-reoxidation is a few mC/cm^2.[85]

One interesting alternative involves the $Ta|Ta_2O_5$ capacitance

electrode suggested by SCHALDACH [81] for possible use in the pacemaker, and subsequently adapted by GUYTON and HAMBRECHT [82] for use in neurogical stimulation. Here the stimulation charge is injected capacitively into the tissue from a Ta electrode *via* a stable protective film of Ta_2O_5. Since the capacity of this (thick) surface oxide is only ~1–2 $\mu F/cm^2$, a microporous electrode composed of fused Ta particles of the order of a few microns in diameter is required. An interesting variation would be to use a $Nb \mid Nb_2O_5$ capacitance electrode operated in a cathodic potential range. Under these conditions, it would be somewhat leaky, but we could take advantage of the high proton–injection "pseudocapacity" reported by VERMILYEA. [83]

Acknowledgments

This work was supported by the National Institute of Neurological Disease and Stroke, National Institutes of Health, Bethesda, Maryland, U.S.A., under Contract NIH–71–2287.

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