Hypodermic Cathode Follower for Drug Administration and Concurrent EEG Recording

By HOWELL I. RUNION and CARL C. RIEDESEL

The development of a stable hypodermic cathode follower has been accomplished for drug administration and concurrent EEG recording. The cathode follower is characterized by grid currents well below 10–11 and an input impedance of approximately 100 meg. ohms. The hypodermic cathode follower is designed to be used in conjunction with a stereotaxic apparatus, thus making it possible to apply drugs to highly localized areas in the vertebrate brain. Simultaneous drug administration and EEG recording are the main features of the instrument and as such offer wide application for neuropharmacology investigations.

DURING THE course of an investigation into the specific sites of action of certain agents which affect central nervous system activity, it was deemed desirable to determine the nature and degree of modification of the electric potential, following administration of microquantities of agents to subcortical sites. Inasmuch as existing instrumentation was not sufficiently discriminatory and introduced the artefact of chronic depolarization, efforts were directed to the development of an instrument to meet certain unique specifications. The detailed design of the equipment which has been a useful addition to the facilities is described in this report.

DISCUSSION

The use of a cathode follower in electrobiology is in itself not a new innovation, but rather a necessity if the investigator is to examine the tissue as closely aligned to its true physiological state as technically possible (1–4). Despite the generally large potentials found in brain tissue (10–500 μv.), the tissue is depolarized easily by excessive grid currents in the input stage of most typical EEG instruments. The cathode follower, with its typically low grid current, becomes a necessity in neuropharmacology if one is recording from subdural regions rather than cortical zones. A variety of cathode followers have been devised to meet the needs of the electrophysiologist; however, it was necessary to develop a unit specifically suited to the intended subdural drug assay approach taken by the authors. The HCF (Fig. 1) is schematically represented in Fig. 2 and may be technically classed as a single ended boot-strapped cathode follower. A more detailed description of the HCF is in the caption to Fig. 2.

HCF Construction.—The HCF was constructed in three parts. The recording head, with the two 6CW4 Nuvistors, was built on a silver chassis that could be attached directly to the stereotaxic electrode carriage (Fig. 1). The cathode d.c. balance and the output d.c. balance controls were built into separate containers for convenience and shielding from 60 c.p.s. interference. All intercircuit connections on the HCF recording head were made using No. 22 solid silver wire and low noise eutectic silver solder.

The HCF is battery operated in all stages of the instrument. The two 6CW4 Nuvistors are series connected in their heater circuits (Fig. 2), as reduction of the heater voltage from its rated 6.3 v. to 3 v. greatly attenuates thermonic noise and at the same time reduces detrimental gas production in the tubes. (Gas tends to increase grid current flow in tubes.) The power is supplied to the recording head from the power pack *via* a multiconductor shielded cable (Fig. 2). The battery supply is housed in a separate enclosed metal chassis (not shown) to reduce electromagnetic interference from being conducted to the recording head.

The authors used the HCF in a monopolar recording configuration. The d.c. balanced output of the HCF is fed into a differential high gain d.c. electron stabilized amplifier or an a.c. differential amplifier, depending on the requirements of the drug analysis.

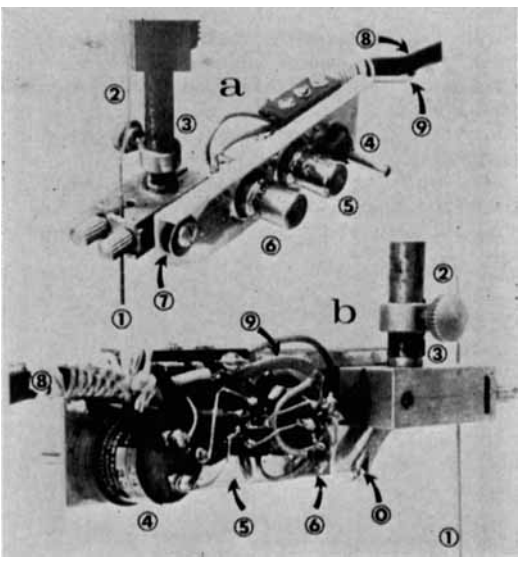

Fig. 1.—The hypodermic cathode follower for concurrent drug administration and EEG recording. Key: (a), front view of the instrument which shows its attachment position to the stereotaxic electrode carriage; (b), rear view of the cathode follower which reveals compact placement of components. 1, Hypodermic electrode; 2, polyethylene drug delivery tube; 3, stereotaxic electrode carriage (Baltimore Instrument Co.); 4, R1, grid current balance control (see Fig. 2 and text); 5, V1, 6CW4 Nuvistor, cathode follower grid current level control, and voltage stabilizer; 6, V2, 6CW4 Nuvistor, cathode follower; 7, cathode follower chassis mounting bolt and insulating fiber washer; 8, power cable; 9, output cable to d.c. balance control box (not shown); 0, cathode follower input. [Lug connects with electrode carriage block and the block is electrically insulated from the rest of the instrument by a fiber-glass ring (not shown).]

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The analysis of the localized EEG is accomplished following differential amplification by the instrument described by Runion (5). The analyzed data are reported in digital form by a Hewlett Packard 522B electronic counter and simultaneously recorded on 35-mm. film and magnetic tape.

Hypodermic Electrode and Drug Delivery Tube.—The hypodermic electrode and drug delivery tube (Fig. 3) is a dual capillary mechanism that makes possible concurrent EEG recording and drug administration. The assembly is stereotaxically placed in the desired subdural regions by a suitable stereotaxic instrument. The hypodermic electrode, which forms the outer shaft for the assembly, is made from a 65-mm. No. 20 gauge hypodermic needle. The hub is removed from the No. 20 gauge needle and the shaft degreased and coated with epoxy resins. The resins are applied inside and out for the full length of the shaft. Except for a 10-mm. area, the top end of the electrode is left bare on the outside. This area comes in contact with the electrode carriage block of the stereotaxic instrument (Fig. 1) and the input lug of the HCF unit (Fig. 1).

The resin coated electrode is baked in an oven at 80° for 5 to 10 hr. After cooling, the electrode is checked optically for insulation breaks. The final check of the electrode is made under dark field illumination with a 40× objective. The electrode is placed in a Ringer's salt solution and a 1.5-v. potential placed across the electrode and the salt bath. Thus, escaping gas can be detected from any broken areas in the insulation of the recording electrode. The tip of the hypodermic electrode is jarred mechanically against a glass slide to chip the epoxy film, thus baring a small area for recording purposes.

The drug delivery tube, used in conjunction with the hypodermic electrode, is prepared from No. 27 stainless steel tubing. The length of the tube is determined by the length of the hypodermic electrode and the additional length required to permit 0.5 mm. of exposure at the tip of the electrode and sufficient tube length for secure connection of the polyethylene delivery tube. The delivery tube, with its polyethylene tubing, is connected to a standard micrometer delivery system. Several drug delivery tubes are used in the programs of drug analysis by the authors. Multiple delivery tubes and micrometer delivery units make possible antagonistic studies in the same subdural site by removal of one drug delivery tube and the insertion of a second without interruption in EEG recording or damage to the preparation.

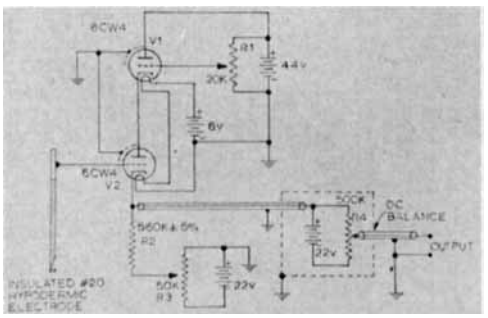

Fig. 2.—Schematic diagram of the hypodermic cathode follower instrument. The instrument technically is classed as a boot-strap cathode follower. V1 and its grid adjustment R1 set the level of grid current seen in V2. The cathode follower, when balanced by R1 and R3, has a grid current of approximately 10–11 or lower, depending on the individual Nuvistors and their aged condition. V1 and V2 are series connected in the heater circuits; thus, the thermal noise level is reduced. The output cable [Fig. 1 (9)] is by Micro Dot, Inc., (orange dot) and is characterized by a solid silver inner conductor, powdered metallic shield, and greatly reduced mechanical noise factors generally found in most coaxial cables. The power supply is all battery as indicated, thus providing lower noise ratio and increased long-term d.c. stability. The noise factor for a shunted input is approximately 1–2 μv. RMS.

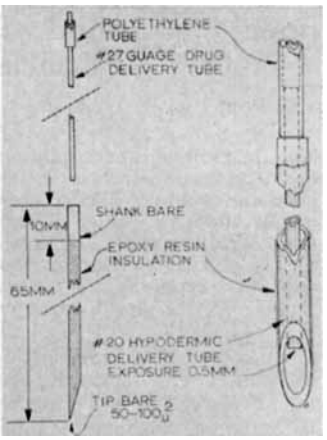

Fig. 3.—The cathode follower hypodermic electrode and drug delivery tube. The hypodermic electrode is made from standard 65-mm. No. 20 gauge hypodermic needle with the hub removed. The needle is insulated along its shaft length inside and out with epoxy resins. A 10-mm. area at the top end of the electrode is left uncoated to make electrical contact with the electrode carriage block [Fig. 1 (3)]. The drug delivery tube is made from No. 27 gauge capillary stock. Its length is determined by fit to the hypodermic electrode. The delivery tube is allowed to extend 0.5 mm. beyond the opening of the hypodermic electrode. The polyethylene tubing acts as a mechanical stop for the No. 27 delivery tube and a means to deliver the drugs from a micrometer dispensing source. The tip of the hypodermic electrode is bared by mechanical means to permit a recording area of 50–100 μ^2. The recording electrode has a d.c. resistance of 500 K — 1 meg. ohms, the range dependent on exposed tip area.

CONCLUSION

The simultaneous investigation of EEG activity and drug activity following administration is made possible with the described cathode follower unit. The instrument is characterized by grid currents of 10–11 and long-term d.c. stability. Used in conjunction with the EEG analysis method of Runion and the interchangeable drug delivery tubes, the instrument opens new areas in pharmacodynamics for the central nervous system and behavior control study programs.

REFERENCES

(1) Spangler, R. A., *Rev. Sci. Inst.*, **33**, 1406(1962).
(2) Dowben, R. M., *ibid.*, **23**, 506(1952).
(3) Vernon, L., unpublished work, University of Oregon, Eugene, Oreg., 1962.
(4) Runion, H. I., *Am. Biol. Teach.*, in press.
(5) Runion, H. I., *Proc. Western Pharm. Soc.*, **7**, 46 (1964).