

UNPUBLISHED 1978

IS THERE A CONNECTION BETWEEN COMA & SPREADING  
CORTICAL DEPRESSION?

Henry C. Tuckwell, Department of Mathematics,

University of British Columbia, Vancouver, B.C., Canada.

Abstract. Multiple and reverberating waves of spreading neuronal depression are discussed as likely concomitants of

Spreading depression of neuronal activity in cortical structures (e.g., cerebral cortex, thalamus, hippocampus, caudate nucleus) manifests itself as a slowly moving (about 3mm/minute) surface-negative potential wave. In some cases the negative phase is preceded by a smaller amplitude positive potential, in others it is followed by a positive phase and sometimes both occur. For many references see Bures et al. (1974).

There are concomitant changes in both neuronal and glial membrane potential (Higashida et al., 1974; Sugaya et al., 1975) together with inward and outward fluxes of sodium, chlorine and potassium ions (Kraig & Nicholson, 1976). The major effect on membrane potential is a depolarization of both types of cells. In glia a sustained depolarization seems to correlate closely with the time course of the surface wave. In neurons (if the tissue has not been treated with tetrodotoxin or any other action-potential blocking agent) rapid spiking usually occurs at the onset of their depolarization after which ~~spiking~~ spiking is completely absent for a few minutes. Depression of neuronal activity in neo-cortex seems to considerably depress the amplitude of EEG.

The mechanisms involved in the instigation and propagation of spreading depression are not yet fully understood. Instigation may be through application of KCl, electrical stimulation, mechanical stimulation or asphyxia (Bures et al., 1974; Shibata & Bures, 1975). Propagation seems to depend mainly on transport of  $K^+$  which by depolarizing post-synaptic membrane, pre-synaptic membrane and non-synaptic membrane leads to further production of  $K^+$ , with or without action potentials. It is possible that glia

play a relatively passive role and that their membrane potential change merely reflects the increase in extra-cellular  $K^+$  concentration due to neuronal sources. A crude mathematical model of spreading depression has been put forward and analysed in which a non-linear diffusion equation for  $K^+$  concentration possesses travelling wave solutions (Grafstein, 1963; Bures et al., 1974), but a satisfactory model, neither qualitative or quantitative has yet been proposed. A more complete model will be proposed by the present authors (Miura & Tuckwell, 1977).

Spreading depression has been utilized primarily as a means of producing the effect of a lesion since de-afferentation or de-efferentation takes place as neurons are rendered inactive. However in an extremely interesting and ingenious set of experiments (Shibata & Bures, 1972, 1974, 1975) waves of spreading depression were made to reverberate around closed paths by introducing an obstacle (lesion) in rat neo-cortex. Initial experiments (Shibata & Bures, 1973) employed a two-stimulus method to start the reverberating wave but later experiments (Shibata & Bures, 1974) have shown that production of a single lesion itself (thermocoagulation) or a single application of KCl can elicit a reverberating wave. The number of circuits of the wave in rat neo-cortex was as high as 55 and termination of the reverberation was attributed to metabolic exhaustion. If the latter did not occur, it is possible that the number of cycles would be much larger than observed.

It seems noteworthy that the conditions which obtain in some methods for eliciting spreading depression are very similar to those which lead to pathological states such as

concussion and coma. Examples of these are mechanical impact, brain damage and the creation of ischemic infarctions. Spreading depression has been observed in man (Bures, 1959) and was postulated by the same author to be a possible concomitant or cause of concussion. The connection between coma and spreading depression has not been discussed.

The term 'coma' is not well defined, though classifications of various states of consciousness from 'normal' through 'stupor' to 'coma' have been made by various authors (Adams, 1970; Stover & Zeiger, 1976; Yamada et al., 1976). The deepest states of coma are usually associated with a complete lack of response to external stimuli. The EEG recordings of comatose patients may be depressed (Yamada et al., 1976) or may exhibit the normal alpha rhythm associated with consciousness in the absence of afferent stimulation in which case the coma is called alpha-coma (Westmoreland et al., 1975). The duration of coma is tremendously variable ranging from almost transient post-epileptic coma through comas which last a day to those which persist for many years. Evidently functional recovery after coma, if it occurs, is better the shorter the duration (Stover & Zeigler, 1976). The etiology of coma is certainly not understood, however, nor has there appeared an effective treatment schedule for comatose patients. This has the exception, however, in cases of diabetic coma (Todd, 1974) where recovery may be quite rapid (Leigh & Shaw, 1976).

Spreading depression does not necessarily lead to loss of consciousness as animals have remained quite alert when the wave has passed through either neo-cortex or hippocampus (Bures, 1959; Bures et al., 1974; Mayevsky and Chance, 1974)

In fact spreading depression in neo-cortex of rats led to an increase in firing rate of some reticular units (Bures, 1959). It is conceivable, however, that a reverberating spreading depression in a structure whose normal functioning was necessary for 'awareness' could lead to loss of consciousness as long as the wave persisted. Since eventually an instability might arise in the wave-form termination of the spreading depression could lead to a return to the conscious state. Such a reverberating wave would require an appropriate lesion to ensure continual passage. One possibility for such a lesion would be lateral cortical necrosis which reflects the selective vulnerability of cells in the middle laminae of the cortex.

We consider, especially in the light of lack of any clinical evidence, that reverberating spreading depression is a remote contender for the cause of comatose behaviour. However it seems very plausible that one or many waves of spreading depression occur during coma.

The threshold concentration of KCl for eliciting spreading depression in rats is about .6% which corresponds closely with the observed maximum level of  $K^+$  during passage of the wave (Kraig & Nicholson, 1976). If higher concentrations of KCl are employed, many waves of spreading depression emanate from the region of application of the chemical. The number of such recurrent or multiple waves elicited is more or less in proportion to the initial concentration. This is in accordance with our observation concerning the data of Mayevsky & Chance (1974) that the waiting times for waves get longer as the

number of waves increases, as this reflects a depletion of the initial concentration of KCl. The mechanism for multiple spreading depression seems to be as follows. The initial stimulus (KCl injection, say) leads to a wave which invades neighbouring populations of neurons which after depolarization of post-, pre- and non-synaptic membrane release  $K^+$ . The diffusion of  $K^+$  from the original source is blocked (it is very slow even in the absence of spreading depression (Bures, 1959)). Then, after recovery of adjacent neurons, some more of the initially applied stimulus can elicit another wave. The shortest time between such waves is about 3 minutes and when these waves quickly follow one another there is little chance for the neurons to return to their normal firing levels.

In comatose patients it would seem that a lesion due to an ischemic infarct or pressure (mechanical stimulation) exerted by a sub-dural hematoma could act as a stimulus for producing multiple spreading depression. The effect need not be local, especially in cases where there are numerous widespread infarctions (Westmoreland et al., 1975). Furthermore, spreading depression in rats has been shown to propagate from one cortical region to another (e.g., from neo-cortex to amygdala and vice-versa) and may appear in a region which is not connected by gray matter with the original region of elicitation (Fifkova & Syka, 1964). In addition, spreading depression in one hemisphere may give rise to a similar wave in the contra-lateral hemisphere (Leao, 1970). Thus there is reason to believe that brain damage could lead to widespread and persistent waves of spreading depression.

During spreading depression there is an increase in metabolic activity of cortical cells (Mayevsky & Chance, 1974). It is interesting that an increase in metabolic activity also has been found to occur in cortex of mice whose brains were damaged with hypodermic needles (Watanabe & Passonneau, 1974). Those authors suggested that an initial spreading depression may have occurred in their experiment. Furthermore a consequent increase in glycogen content was observed and we note that hyperglycemia is a concomitant of spreading depression (Bures, 1959). For further studies of metabolic activity during coma see Rudman et al. (1976) where cyclic AMP levels were found to negatively correlate with depth of coma.

It is concluded that conditions for eliciting spreading depression certainly exist in the brains of many comatose patients and that known measurements of metabolic activity during coma correspond with those obtained during spreading depression. It is possible that known methods for blocking spreading depression (Shibata & Bures, 1975), such as the application of  $\text{CaCl}_2$  or  $\text{MgCl}_2$ , or temporary asphyxia, may lead to an alleviation of the comatose condition by preventing the concomitant increase in metabolic activity. This might enable recovery from coma to proceed at a faster rate.

We acknowledge useful discussions and references due to Dr K. Berry, Vancouver General Hospital, Dr R. R. A. Brock, Florey Clinic, Adelaide, Dr D. M. J. Quastel, Department of Pharmacology, University of British Columbia.

REFERENCES

- Adams, R.D. (1970). In 'Harrison's Principles of Internal Medicine'.  
New York: McGraw Hill.
- Bures, J. (1959). In 'The Central Nervous System and Behavior'. M.A.B.  
Brazier (Ed.).
- Bures, J., Buresova, O., & Krivanek, J. (1974). 'The Mechanism and  
Applications of Leao's Spreading Depression of Electroencephal-  
ographic Activity'. New York: Academic Press.
- Fifkova, E. & Syka, J. (1964). *Exptl. Neurology* **2**, 355.
- Grafstein, B. (1963).
- Higashida, H., Mitarai, G. & Watanabe, S. (1974). *Brain Research* **65**, 411.
- Kraig, R.P. & Nicholson, C. (1976). Society for Neuroscience Abstracts,  
Toronto.
- Leao, A. (1970). In 'Experimental Models for Epilepsy'.
- Leigh, R.J. & Shaw, D.A. (1976). *Arch. Neurol.* **33**, 356.
- Mayensky, A. & Chance, B. (1974). *Brain Research* **65**, 529.
- Miura, R.M. & Tuckwell, H.C. (1977). *Not. Amer. Math. Soc. (abstr.)*, to appear.
- Rudman, D., Fleischer, A. & Kutner, M.H. (1976). *New Eng. J. Med.* **295**, 635.
- Shibata, M. & Bures, J. (1972). *J. Neurophysiol.* **35**, 381.
- Shibata, M. & Bures, J. (1974). *J. Neurobiol.* **5**, 107.
- Shibata, M. & Bures, J. (1975). *J. Neurophysiol.* **38**, 158.
- Stover, S.L., & Zeiger, H.E. (1976). *Arch. Phys. Med. Rehabil.* **57**, 201.
- Sugaya, E., Takato, M. & Noda, Y. (1975). *J. Neurophysiol.* **38**, 822.
- Todd, J.W. (1974). *Brit. Med. J.*, August, 471.

Watanabe, H. & Passonneau, J. V. (1974). Brain Research 66, 147.

Westmoreland, B. F., Klass, D. W., Sharbrough, F. W., & Reagan, T. J. (1975).

Arch. Neurol. 32, 713.

Yamada, T., Tucker, R. P., & Kooi, K. A. (1976). Electroenceph. Clin.

Neurophysiol. 40, 645.