Hypothesis

AN EXTENDED MESSENGER-ROLE IN THE BRAIN FOR CYCLIC AMP

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1. Introduction

Adenosine 3′,5′-monophosphate (cyclic AMP) when added to or generated in several neural systems modifies their cell-firing and consequent activity [1,2], and is pictured to do so by activating protein kinases which control ion movements [3,4] so altering cell-polarization and discharge. Only small quantities of cyclic AMP are needed for this, such as can be calculated to be formed by a single stimulating pulse or in a few msec. [5]. Cell-firing in the brain is frequently continuous or repetitive, and under such circumstances cyclic AMP accumulates; stimulation in vitro raises its concentration from 1 to 30 or 40 nmol/g [6]. Studies with labelled precursors give evidence for locally increased concentrations 20 times these values [5,7,8]. After such increase, cyclic AMP can be visualized in nerve-cell bodies by immuno-fluorescence techniques [9] and remains above its original level for at least 10 to 30 min [7,10].

2. Hypothesis

It is now postulated that cyclic AMP travels along nerve cell axons and dendrites during this 10 min or more, reaching further sites where, again, it conditions cell-discharge and consequent phenomena.

The following points indicate the feasibility of this proposal. It is inherent in the action of cyclic AMP as an intracellular messenger that it migrate across normal cellular distances in reaching, e.g., ribosomes, the nucleus or other organelles [11]. The suggestion [3,4] that in conditioning cell-firing cyclic AMP acts at membrane proteins which are immediately adjacent or contiguous to its site of generation, is not a general feature in its action, though it is relevant if very prompt neural action is the main characteristic to be explained. The phosphodiesterases which normally limit the action of cyclic AMP by hydrolysing it are subject to complex activation and control in neural systems [11]. A soluble, cytoplasmic, enzyme has relatively low affinity for cyclic AMP: apparent K_M, approx. 1 mM [12], which is consistent with the persistence of moderate concentrations of the nucleotide. A subsynaptic, membrane-bound enzyme is of high affinity: apparent K_M for cyclic AMP, about 1 μM [13]; movement of cyclic AMP away from its membrane-site of generation thus removes it from a major site where loss may occur.

Intracellular movements of adenine nucleotides were postulated on finding that nerve terminal preparations from the neocortex released adenine derivatives, including cyclic AMP, in quantities up to 1.5% of their content/min [14–16] whereas generation of cyclic AMP was most readily seen at nerve cell bodies [9]. Axonal and dendritic flow of adenine nucleotides has indeed been observed by autoradiographic methods [17,18] occurring at rates of some 15–60 μm/min in cerebral or spinal neurons of cats and rabbits. Many functions are performed by such cytoplasmic flow in neural systems (table 1), including some concerning neurotransmitters, but the movement of cyclic AMP is distinct from these in bringing the already active second messenger to its site of action without the need for release by further stimulation. Cytoplasmic flow of cyclic AMP thus constitutes a slowly-moving nerve-signal, travelling at 0.25 to 1 μm/sec in contrast to the 1–100 m/sec of the orthodox nerve impulse. 'Readout' of the signal is pictured to occur at the

Table 1
Cytoplasmic movement of a second messenger

Recognized roles for cytoplasmic flow [16–19]

1. Supply from the cell body of metabolites, enzymes, ribonucleic acid, organelles.
2. Transport to the cell body of materials for re-use; retrograde movement of substances participating in control of protein and ribonucleic acid synthesis.
3. Movement of neurotransmitters including acetylcholine and catecholamines, free or vesiculated. To act, these require (i) release by nerve impulse; (ii) travel to extracellular sites.

Now proposed

Cyclic AMP which is formed intracellularly near its primary site of action, may act: (i) locally; and (ii) at other sites after translocation by axonal or dendritic flow: so constituting, without further mechanism for release or activation, a nerve-signal travelling at 15–60 μm/min.

many sites at which cyclic AMP (locally generated) is already considered [3,4] to activate protein kinases controlling membrane permeability: this simplification is specific to 'second messengers' akin to cyclic AMP. Mobile protein kinase complexes have been suggested as mediating some intracellular actions of cyclic AMP [20] and the proposals of Table 1 may be extended in an analogous way.

Comment

Recognition of a slowly-moving neural signal can assist interpretation of cell-firing patterns in the brain. Thus mammalian cerebellar Purkinje cells [21,22] receive among their inputs noradrenergic innervation, stimulation of which augments their cyclic AMP [9] in association with concomitant changes in firing rates. Fluctuations in their firing rates occur also over periods lasting from a few seconds to several minutes and are not readily interpreted [22]; they however vary with cell activation which has occurred earlier. The cells carry dendritic trees extending up to 100 μm from the cell body [23]; cyclic AMP proceeding as in table 1 would traverse this distance in 1.6 to 6 min and during this time, by present proposals, could modify cell firing. The channel-capacity of nerve axons for transmission by electrical impulses is large but limited [24] and the complementary mode of transmission proposed in table 1 merits exploration in other cerebral processes which occupy some minutes or more, as shortterm memory [25] and aspects of problem-solving [26].

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