A Theory of the Mechanism of Cerebral Vasospasm and Its Reversal, the Role of Calcium and Cyclic AMP

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SUMMARY: It is proposed that the basic mechanism of vasospasm which sometimes follows subarachnoid hemorrhage is dependent on increased free intracellular calcium ion produced by spasmogens from closely applied extravasated blood. Relaxation of this spasm occurs when the intracellular cyclic AMP levels are raised, resulting in sequestration of calcium ion by the vascular smooth muscle cell sarcoplasmic reticulum.

RÉSUMÉ: Il est proposé que le mécanisme de base du vasospasme, qui quelquefois suit l'hémorragie méningée, est dépendant de l'augmentation de l'ion calcium intracellulaire produit par spasmogènes provenant de sang extravasé appliqué à proximité. Le relâchement de ce spasme se produit quand les niveaux d'AMP-cyclique intracellulaires sont élevés, résultant en une séquestration de l'ion calcium par le réticulum sarcoplasmique des cellules musculaires lisses vasculaires.

In the last three decades, the reactivity of cerebral blood vessels to subarachnoid hemorrhage has been widely recognized (Ecker and Riemenschneider, 1951). This vasospasm is commonly seen following rupture of an intracranial aneurysm of the Circle of Willis. Since this complication usually occurs after an interval of five to seven days, operative treatment is preferably delayed for a week or more, thereby increasing the danger of re-bleeding from an unclipped aneurysm. In a recent review of 321 consecutive cases, 18% of patients died of re-bleeding before operation could be performed (Drake, 1976). Once spasm is established, ischemic necrosis of the brain may occur and, combined with the problems attendant upon a bleeding aneurysm, may prove fatal. Further progress in the management of ruptured intracranial aneurysms therefore, awaits an effective approach for the prevention or reversal of vasospasm. We proposed (Peterson et al, 1973a, 1973b, 1973c, 1973d, 1975a) that the manipulation of the vascular smooth muscle adenylate cyclase-cyclic AMP system, either by phosphodiesterase inhibition with topically applied theophylline or by the exogenous supply of cyclic AMP as its dibutyryl derivative might modify cerebral vascular constriction that sometimes follows subarachnoid hemorrhage.

A number of physiological factors affect the internal diameter of cerebral blood vessels (Kapp, 1968). Catecholamine fluorescence (Peerless and Ysargil, 1971) and \( \alpha \) and \( \beta \) receptors have been described (Lowe and Gilboe, 1971; Edvinson and Owman, 1974), but the role of the sympathetic nervous system in this condition remains controversial (Langfitt, 1974). The probable source of spasm initiating factors is the adherent blood clot enmeshed in the subarachnoid trabeculae, and the platelets in this clot (Kapp, 1968) are thought to produce the two putative spasmogens, serotonin (Echlin, 1968) and prostaglandin \( \text{F}_2 \alpha \) (PGF\(_2 \alpha \)) (White et al, 1975).

Prostaglandins are a heterogeneous group of ubiquitous naturally occurring long chain fatty acids capable of exerting a wide variety of actions in different tissues and in different species. Prostaglandin \( \text{E}_1 \) has been shown to increase the levels of cyclic AMP (Borgeat et al, 1975) in many preparations by its action on adenylate cyclase, the enzyme that produces cyclic 3'5' AMP (cyclic AMP) from ATP. The consensus of most investigators is that this substance has a vasodilating effect (Pelofoxy et al, 1972). Prostaglandin \( \text{F}_2 \alpha \) has only a very slight effect on the level of cyclic AMP (Borgeat et al, 1975; Barrett-Bee and Green, 1975) in many systems, but this is probably irrelevant to its action on cerebral blood vessels. It is well established as a spasmogen in experimental vasospasm (White et al, 1975) and requires the presence of extracellular calcium ion to exert its effect (Allen et al, 1976). Possibly the mechanism of action of PGF\(_2 \alpha \) is increased cellular permeability to calcium ion (Goodman and Gilman, 1970). Thrombin stimulates the formation of it from platelets and it is also produced by brain tissue. In addition, serotonin increases PGF\(_2 \alpha \) synthesis (White et al, 1975). Prostaglandin \( \text{F}_2 \alpha \) can be produced at the involved site by many mechanisms and experimental evidence demonstrates potent vasoconstrictor properties in many animal
models indicating a possible role in the genesis of cerebral vasospasm (White et al., 1975). However, determinations of the presence of prostaglandin F: \( \alpha \) in the CSF in cerebrovascular disease (LaTorre et al., 1974; Wolfe and Namer, 1975) are inconclusive. These samples of CSF were obtained from the lumbar subarachnoid space and therefore they cannot properly reflect the concentration of the spasmogen in the closely applied and degenerating clot at the base of the brain.

Serotonin is widely distributed. In man, 90% occurs in the GI tract, 8-10% in platelets and only 1-2% exists in the central nervous system (Cooper et al., 1974). Although Kapp thought that the platelet spasmogen was not serotonin, it has been implicated by others (Pool, 1958) and has recently been extensively investigated (Allen et al., 1974). Serotonin induced vasospasm is also dependent on extracellular calcium ion (Allen et al., 1976).

We can affirm that cerebral vasospasm occurs frequently after subarachnoid hemorrhage, that it is a serious condition, and that the problems occasioned by it are associated with a high mortality. Spasm is seen in association with blood in the subarachnoid space, where the thin walled and naked cerebral blood vessels lack a well developed adventitia and have no vasa vasorum (Fisher). Because the walls lack perfusion by their own capillaries to clear effective concentrations of stimulating substances, cerebral vascular smooth muscle cells are probably vulnerable to vasoactive agents originating in the adherent blood clot in the subarachnoid space. The substances frequently implicated are prostaglandin F: \( \alpha \) and serotonin, both produced by platelets, both requiring extracellular calcium, and both increasing cellular calcium permeability (White et al., 1975).

We have postulated that increasing the cyclic AMP content of the spastic smooth muscle cell would also result in the reversal of established spasm, and we reported these observations using theophylline and dibutryl cyclic AMP (Peterson et al., 1973a, 1973b, 1973c, 1973d). Recently, this has been confirmed by others (Flamm, 1975). Papaverine, a widely used vasodilator, is a potent phosphodiesterase inhibitor (Triner et al., 1970) and may exert its action by increasing the cyclic AMP of the vascular smooth muscle cell. We have recently established that increasing the intracellular cyclic AMP levels by topical application of dibutryl cyclic AMP can reverse prostaglandin F: \( \alpha \) induced spasm (Peterson et al., 1975b) of the basilar artery of the cat. Cyclic AMP is also a ubiquitous substance with many effects, and has been characterized as the “second messenger” in the action of many hormones (Robison et al., 1971a). It is synthetized from adenylyl cyclase (thought to be the \( \beta \) receptor [Robinson et al., 1971b]), from ATP, and is degraded by phosphodiesterase to 5’AMP. There are three ways of increasing cellular cyclic AMP content; by stimulation, by phosphodiesterase inhibition and by exogenous supply of cyclic AMP in its dibutryl form. Norepinephrine and dopamine act in the central nervous system by the alteration of the post-synaptic cyclic AMP levels (Cooper, 1975).

One of the actions of cyclic AMP is to decrease the availability of intracellular free calcium ion. Anderson (1972) believes that cyclic AMP may produce its relaxing effect by stimulating the calcium binding processes in the smooth muscle cell and in reducing the free myoplasmic calcium ion. Vascular smooth muscle contraction depends on the coupling of the contractile proteins, actin and myosin (Somlyo and Somlyo, 1970; Bohr, 1973). Myosin, the thick filament, has laterally projecting cross bridges extending towards the nearby thin actin filaments, which appear to be attached to dense bodies related to the cell membrane. Contraction would take place in a manner analogous to the sliding filament theory of skeletal muscle, where interaction between myosin and actin filaments using chemical energy derived from ATP hydrolysis results in mechanical work. This reaction is calcium dependent, but other less well understood factors, such as magnesium ion concentration, sodium ion concentration and fiber length are involved. Thus the contraction seen following mechanical irritation of cerebral blood vessels during operation, might be the result of alteration of fiber length.
which is a determinant of the force
exerted by the contractile proteins
(Bohr, 1973). Calcium ions may be
stored in the intracellular or extracellular
calcium and the main-
induced contraction requires cal-
cium ions from both sources, the
first response being dependent on
intracellular calcium and the main-
tained slower response on extracel-
lar calcium (Bohr, 1973). This
might be relevant to the contraction
produced by mechanical stimulation
(Arutinov et al, 1974).

The sarcoplasmic reticulum acts
as an intracellular store of calcium
which it supplies or removes from
the vicinity of the contractile pro-
teins. Contraction or relaxation of
vascular smooth muscle is depen-
dent on the availability of the ap-
propriate concentrations of this ion.
The available calcium ion is influ-
enced by the influx from extracellu-
lar supplies or by the extrusion of
the intracellular ion, or by its se-
questration or release by the sarco-
plasmic reticulum. Relaxation of
the myocardium involves activation of
adenylyl cyclase resulting in an in-
crease in cyclic AMP which has the
ability to stimulate calcium ion se-
questration by sarcoplasmic re-
ticulum. This is accomplished by the
activation of a cyclic AMP depen-
dent protein kinase that catalyses the
phosphorylation of various pro-
teins and results in stimulation of
calcium ion transport into the sarco-
plasmic reticulum (Katz, 1975).
Serotonin or prostaglandin F₂α in-
duced spasm is dependent on ex-
tracellular calcium ion (Allen et al,
1975). By contrast, EDTA has a
vasodilating action in blood induced
spasm of the basilar artery of the cat
by chelating calcium (Peterson,
1968).

Cerebral vasospasm can be con-
dered to be a calcium ion dependent
activation of actin and myosin cou-
pling. Relaxation of vascular smooth
muscle can be considered to be de-
pendent on increased levels of in-
tracellular cyclic AMP.

Serotonin is known to increase the
activity of adenylyl cyclase in some
preparations and to decrease it in
others (Goodman and Gilman, 1970;
Blum, 1970), but, a membrane activ-
ity of serotonin resulting in calcium
entry into the cell is generally consi-
dered to be responsible for smooth
muscle contraction. This effect is
thought to be due to increased mem-
brane permeability allowing calcium
ion to run passively down its elec-
trochemical gradient (Goodman and
Gilman, 1970) because in resting
muscle, the intracellular calcium ion
concentration is 10⁻⁷M, while the
extracellular pool concentration is
10⁻⁵M (Bohr, 1973). It has been
thought that the effects of prostag-
landins were a general modulation of
adenylyl cyclase activity (Good-
man and Gilman, 1970) and this
thinking was the basis of our expla-
nation of the spasmogenic effect of
prostaglandin F₂α (Peterson et al,
1975b). Although it is true that some
prostaglandins have a very marked
effect on adenylyl cyclase (prostag-
landin E₁ in particular markedly in-
creases the activity of this enzyme),
this modulation does not seem to be
the mechanism of action of prostag-
landin F₂α (Borgeat et al, 1975;
Barrett-Bee and Green, 1975;
Rather, it has been suggested that
prostaglandin F₂α increases cellular
permeability to calcium ion and this
is the basis for its spasmogenic ac-
tivity. It has been postulated that these
agents and possibly other spas-
mogens could exert their effect by
increasing calcium ion influx into the
vascular smooth muscle cell from
extracellular sources and thus ren-
der calcium available for action and
myosin coupling. Spasm could be
maintained by the clot adjacent to
the involved artery releasing a con-
tinuous supply of an effective con-
centration of the spasmogen. This
could also explain the usual delay in
the appearance of spasm for 5-7 days
while effective concentrations were
accumulating in the degenerating
clot. The possible removal of these
substances could be hindered by the
hemorrhage blocking the CSF path-
ways at the base of the brain. If there
is an increased level of cyclic AMP
in the cell by topical application of
dibutyryl cyclic AMP or by β
stimulation or by phosphodiesterase
inhibition, there would be a de-
creased calcium ion concentration
permitting ATP to be used to ener-
gize the actin-myosin decoupling
with resultant vasodilatation.

Parenteral administration of β
agonists or phosphodiesterase in-
hibitors could not be expected to
reverse established spasm, because
the lack of vasa vasorum precludes the
attainment of effective concentra-
tions of cyclic AMP within the
cell. However, prophylactic treat-
ment of patients with bleeding
aneurysms with β stimulation
and/or phosphodiesterase inhibition
may in time accumulate enough of
these agents to increase cyclic AMP
levels in those cells exposed to ex-
travasated blood. This might result
in a less severe or less prolonged
spasm. The effects of such a
therapeutic regimen would also be
felt systemically, but the topical ap-
lication of drugs at the time of
operation would be more restricted.
We have observed that the intracri-
ternal injections of dibutryl cyclic
AMP in cats and in monkeys, while
effectively reversing blood induced
vasospasm, also have resulted in
epileptic seizures which seem to
originate in the hippocampus. These
were controlled by diazepam (Pet-
erson et al, 1975b). This route of ad-
ministration is not satisfactory for
clinical treatment at present.

In summary, we propose that vas-
osspasm may be considered a re-
tion by vascular smooth muscle,
whereby under the influence of cer-
tain substances, an increase in the
calcium ion concentration occurs in-
side the cell, resulting in actin and
myosin coupling. It can be pro-
longed if there is a continued supply
of spasmogen from extravasated and
degenerating blood. Relaxation oc-
curs when there is a decrease in the
intracellular calcium ion concentra-
tion due to the cyclic AMP medi-
ated sequestration of this ion by the sar-
coplasmic reticulum.

REFERENCES

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