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ARTERIAL WALL CHANGES IN CHRONIC CEREBROVASOSPASM: IN VITRO AND IN VIVO PHARMACOLOGICAL EVIDENCE[1]

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INTRODUCTION

Chronic cerebrovasospasm is the term used to describe a narrowing of one or more cerebral arteries that reverses over a period of several weeks. The condition is of concern because of its association with neurological deficit, the consequence of cerebral ischemia and sometimes infarction. The spasm is usually a complication of subarachnoid hemorrhage, which in the majority of instances results from the rupture of an intracranial aneurysm. There are about 30,000 cases of subarachnoid hemorrhage in the United States per year (1), and vasospasm is a major cause of mortality and morbidity. Demonstrated clinically only by angiography, chronic spasm is usually manifest about four days after the hemorrhage, reaching its peak a few days later. It sometimes occurs without clinical evidence of ischemia. Such variation undoubtedly reflects the limitation of diagnostic techniques to demonstrate narrowing, when it occurs in smaller arteries, or variability in the vascular perfusion reserve that can occur through collateral channels. Vasospasm is generally reported to be refractory to vasodilator pharmacological therapy.

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As the basis of the arterial narrowing has not been established, the initiating causes and the sequence of events leading to the condition are matters of speculation.

This chapter is not concerned with the diagnosis, prognosis, clinical management or risk assessment of the chronic vasospasm, but rather with the results of the use of pharmacological agents in the human condition and in animal models. These represent one source of clinical and experimental information that must be taken into consideration when trying to understand the genesis and basis of the condition. The effects and lack of effects of these drugs are cited in support of a hypothesis about the pathogenesis and pathophysiology of vasospasm.

Only literature published prior to May, 1987, is treated in this review.

PATHOGENESIS AND PATHOPHYSIOLOGY OF CHRONIC CEREBROVASOSPASM: A HYPOTHESIS

Chronic cerebrovasospasm arises from the damage to the vascular smooth muscle and possibly to other cellular elements of the artery wall that occurs within a day or two of aneurysmal rupture and hemorrhage (Figure 1). Damage is probably caused by one or more of a variety of substances derived from blood clot and damaged local tissue. The immediate effect of these substances, which may be additive or even synergistic, is extreme vasoconstriction most likely involving physiologically relevant systems and mechanisms. Evidence of vascular wall damage is abnormal smooth muscle function such as spontaneous, often irregular increases in vascular smooth muscle tone. When it is more severe, pathological changes, including cell death, an inflammatory response with edema of the vascular wall and fibrosis, occur. This results in increased rigidity of the artery wall, and a vessel whose diameter is much less than normal when distended by physiological intravascular pressures. The relative contribution of these two types of changes: abnormal spontaneous activity of smooth muscle and decreased compliance of the artery wall, varies among individuals and in different vessels in the same individual depending on the pattern and extent of arterial damage. The sequence of events translates into an immediate active phase of vasoconstriction that can be temporarily ameliorated by pharmacological dilators of all types and is the basis of the initial phase of vasospasm, or at least of early cerebral artery narrowing. The second phase of vasospasm is relatively refractory to vasodilator drugs and reflects pathological changes in the artery wall. Our hypothesis (see Figure 1) implies that the second phase is initiated during, and grows out of early events, and that the chronic phase can only be reduced by interference with the initial changes that give rise to it.

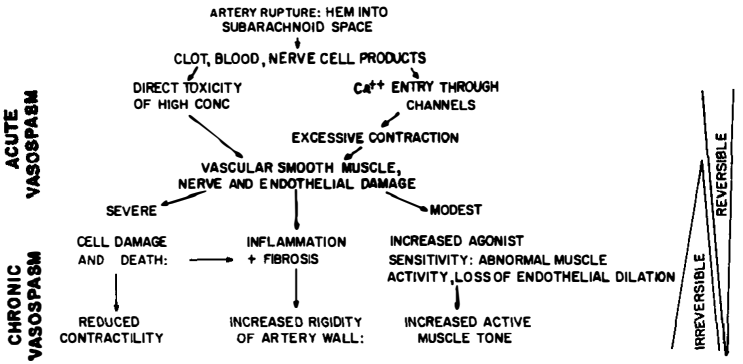

Figure 1 Diagram of suggested sequence of events in the development of chronic vasospasm.

Because of space limitation, this review only covers studies that are particularly relevant to the proposed hypothesis, and special attention is given to the inferences that can be made from the use of drugs. Although there is general agreement regarding the features of the clinical state and its manifestations, confusion exists about the use of the terms *cerebrovasospasm* and *chronic cerebrovasospasm* in the experimental context. The terms are not always appropriate to describe the narrowing encountered in various experimental animal models. There is little reason to think that the acute effects observed upon the application of a vasoconstrictor to an exposed cerebral artery during surgery or to an in vitro preparation have any relevance to the chronic narrowing that occurs clinically. Such experiments may well have relevance to the processes involved in the initial vasospasm, i.e. the immediate narrowing that follows subarachnoid hemorrhage, but only to that phase. Similarily, arterial narrowing is observed by means of angiography in animal models only one or two days after they have been subjected to a procedure mimicking subarachnoid hemorrhage that is reversed by vasodilator drugs. However, it almost certainly does not have the same basis as the arterial narrowing demonstrated in most patients by angiography and associated with cerebral ischemia. Refractoriness to vasodilator therapy is the hallmark of arterial narrowing that is of clinical concern and has been established in countless patients by clinical observation over many decades. This feature of the phenomenon is the prime motivation for research. Unless there is some supporting evidence that large vessel narrowing in animal models has characteristics that are at least partly indicative of chronic cerebrovasospasm, we have not cited such experimental findings.

For a more detailed discussion of cerebrovasospasm, particularly from

a clinical point of view, the reader can consult several excellent reviews (2–4).

ANIMAL MODELS OF CEREBROVASOSPASM

An appropriate animal model of vasospasm should reflect the salient features of the clinical syndrome and provide opportunities for experimental measurement and manipulation. The value of a model is only as great as the clarity with which it achieves these goals. Frazee's monkey model (5) has a number of attributes that commend its use and justify confidence in the subsequent findings. After hemorrhage caused by withdrawal of a needle previously passed through the wall of the internal carotid artery, a widespread, mainly ipsilateral spasm occurs that is long lasting, reaches a maximum after about one week, and invariably involves associated neurological deficit. The narrowing is ameliorated only in part by high concentrations of nitrites (6), a finding consistent with clinical observation (7). This small but significant effect of a vasodilator is consistent with in vitro studies of the affected arteries, which suggests that chronic vasospasm has varying proportions of pharmacologically reversible and irreversible components (see below). The cerebral circulation of the primate, similar to the human, is large enough to permit the necessary resolution in angiography and adequate in vitro examination of arterial segments.

A variety of other experimental preparations of vasospasm have been developed in the monkey, and also the baboon, cat, dog, rat, and rabbit. Subarachnoid hemorhage is mimicked by blood injected around the vessels at the base of the brain or by inducing local hemorrhage by rupture of a large cerebral artery. Although none of these shows as many of the essential clinical aspects as the Frazee model, a great deal of extremely important information has been obtained from their use. It seems likely that as the basis of chronic cerebrovasospasm becomes more clear, other models in smaller animals can be used to investigate specific questions.

CHRONIC, IRREVERSIBLE CEREBROVASOSPASM

We propose that the irreversible component of chronic narrowing is due primarily to structural change in the cerebral artery wall resulting from cell damage, and that these changes are particularly important in the region of the clot. Abnormal myogenic activity, that part of the narrowing that can probably be reduced by vasodilators, may be of little consequence in the region

close to the clot but relatively more important distally. The following arguments support this thesis.

Failure of Vasodilator Drugs in Humans

Wilkins (2, 3) has ably summarized in a comprehensive table attempts made to relieve chronic vasospasm by using pharmacological agents that would be expected to cause cerebrovascular vasodilation. He states in conclusion that "attempts to dilate narrowed intracranial arteries have not been successful in the human."

The following pharmacological classes have been examined (for details and references see Wilkins (3), from whom the list below has been obtained):

1. Drugs that dilate cerebral arteries or antagonize their constriction. These include β-adrenoceptor agonists, α-adrenoceptor antagonists, β-adrenoceptor antagonists, agents causing acute sympathetic denervation, parasympathomimetics, postganglionic cholinergic antagonists, serotonin antagonists, nitrites, phosphodiesterase inhibitors, prostaglandins and agents that influence prostaglandin-related processes, nonsteroidal anti-inflammatory drugs, antiplatelet drugs, adenosine-like compounds, free radical scavengers, local anesthetics, calcium channel antagonists, papaverine and related compounds, plus a variety of miscellaneous compounds including calmodulin antagonists, histamine, angiotensin, converting enzyme inhibitors, ethanol, etc.
2. Drugs used to prevent fibrinolysis.
3. Drugs and procedures that neutralize vasospastic effects of clotted blood.
4. Drugs used to reduce focal acidosis.
5. Procedures, including drugs, that interrupt sympathetic monoaminergic pathways.

The only conclusion that can be drawn from this research is that chronic vasospasm is a condition which, once established, is not improved by drugs that would be expected, upon acute or subacute administration, to decrease "normal" vascular smooth muscle tone.

Failure of Vasodilator Drugs in Animals

Delayed cerebrovasospasm can be produced in dogs by injections of blood into the cisterna magna at intervals of two days (8). The subsequent intractable vasoconstriction is accompanied by structural changes that include corrugation of the endothelium, vacuolation of endothelium and the vascular smooth muscle cells, myonecrosis, and edema. Blood clot products were found in the artery wall. Consistent neurological changes were not seen in this

study, although some of the dogs were drowsy and had a staggering gait on day 5.

Intravenous aminophylline, nifedipine, and intra-arterial papaverine failed to dilate the constricted arteries after the second injection of blood. Lack of effect from vasodilator drugs in animal models of vasospasm has frequently been reported. However, without independent corroborative information on the state of the artery and strong support for the validity of the experimental model, the persuasive value of such findings is equivocal.

Quantitative Evidence That Changes in Passive Properties in the Arterial Wall Can Account for Arterial Narrowing

Nagasawa et al (9) measured elastic properties of dog cerebral arteries after autologous blood had been injected intracisternally. After two days, the vessels were more distensible but then became progressively stiffer, owing, the authors propose, to an increase in mural collagen. The change in the passive length-force curve was linked with the arterial collagen/elastin ratio. In this study spasm was not proved. One possible explanation of why the arteries were less stiff is that the length/force studies were carried out with segments that possessed some active smooth muscle tone. Smooth muscle is more distensible than other components of the artery wall.

In vitro examination of arteries from the monkey model 5–6 days after hemorrhage (10) showed consistent evidence of increased wall stiffness (decreased compliance) of segments of the anterior and middle cerebral artery wall compared with that of the contralateral side. The mean increase of 14% in wall thickness was significant but small. Modelling of the consequences of this increased stiffness, considered together with the variety of other changes encountered in this study (11), demonstrated that increased stiffness alone could account for the arterial narrowing to about 60% of control and would result in an 80% reduction of blood flow. It may be only coincidental that the mean angiographic diameter at the sites from which arterial segments were taken for examination of their passive properties was 61 ± 5% of corresponding sites on the contralateral side.

Relation of Angiographic Narrowing to Arterial Damage

Extrapolation from in vitro experiments on arterial segments to the in vivo state is fraught with problems. However, in this regard the monkey spasm studies have the advantage that a specific artery segment whose diameter has been measured by angiography can subsequently be studied in vitro. Wall stiffness cannot be quantitatively related to narrowing for a variety of reasons; the most important is lack of information on intra-arterial pressure during

angiography in the segment studied. It seems reasonable, though, to assume that "contractility," the ability to contract maximally in response to any agonist, is an index of the survival of the artery wall after damage. In the monkey model, maximum contractility of the artery segment is a positive function of arterial diameter of the spastic vessel during angiography, expressed as percent of control. The greater the narrowing during angiography, the greater the loss of contractility in vitro, and vice versa. This implies that the greater the damage is, the greater is the arterial narrowing; i.e. the greatest narrowing occurs in segments that have the least capacity to contract (12). Presumably, the greater the damage, the greater the increase in wall stiffness.

This finding has a number of implications. The most important one is that changes in active tone cannot form a basis for severe vasospasm. At least in this model, perivascular vasoactive material, no matter what its source, cannot account for the arterial narrowing. Furthermore, increased agonist sensitivity of smooth muscle cells, such as occurs upon denervation (13) , and loss of chronic vasodilator influence from the endothelium and dilator perivascular nerves—both factors that might increase active smooth muscle tone—must be of lesser importance. Such considerations would also exclude an important role of myofibroblast contraction (14).

Toda et al (15) studied at seven days a dog model of subarachnoid hemorrhage that occurs secondary to rupture of the internal carotid artery. At this time arterial narrowing could be demonstrated by angiography. Large decreases in contractility of isolated arterial preparations in response to all agonists studied occurred particularly on the side of the lesion. Other details of the spasm are not described. These findings are consistent with nonspecific damage, as was the finding that recovery had occurred by 42 days. Evidence that damage to arteries is associated with decreased contractility has been emphasized in studies by Chayatte & Sundt (16).

Arterial narrowing that is not reversible by vasodilators is not necessarily the result of fibrosis, edema, and associated passive changes in the artery wall. Duckles et al (17) found that, when stretched to twice its length, the rabbit basilar artery developed localized constrictions that persisted up to 72 hours, which is as long as they were studied. Areas of constriction were related to rupture of the internal elastic lamina and disorganization of the adjacent media. Once established, contractions were not reversed by cyanide or by calcium depletion, although these prevented their genesis.

Evidence of Structural Damage From Animal Models and Humans

Although not all investigators have observed ultrastructural changes in human biopsy material (18, 19), there is considerable agreement about the structural

alterations in the artery wall associated with chronic human spasm. It is not necessary to present these in detail here, but only to state that changes occur that are consistent with decreased contractility, increased rigidity, and narrowing that evolves over a period of days. These include changes in smooth muscle cells such as vacuolation, mitochondrial degeneration, and cell necrosis; neuronal degeneration; intimal swelling including subintimal fibrosis; endothelial vacuolation; and infiltration of inflammatory cells, including macrophages, lymphocytes, and plasma cells (13, 14, 20–28).

Briefly, the following structural changes were seen in anterior cerebral artery segments in the vicinity of the lesion in a monkey model of subarachnoid hemorrhage after 5 days: small adherent organizing blood clots and an inflammatory cell infiltration of the adventitia, particularly by macrophages was observed; varying degrees of edema, cell injury, and degenerative changes were present involving peri-adventitial nerve bundles, nerve terminals, smooth muscle and endothelial cells; increased collagen was present in the adventitia (11).

Role of Abnormal Tone Activity

In the monkey subarachnoid hemorrhage model, abnormal, apparently spontaneous, periodic increases in smooth muscle tone were observed not only in arterial segments from the vicinity of clot, but in the smaller pial arteries as well. These changes were very significantly less in the diltiazem-treated animals (10, 29). It is our impression that narrowing of the large cerebral arteries on the side of the hemorrhage was mainly passive. Tonic activity would contribute relatively more to narrowing in the smaller, more distal branches of the cerebral arteries. The role of this activity in vivo is difficult to assess. Considerable narrowing of the roots of the larger arteries would reduce dye entry into the smaller, more distal vessels. This possibility makes questionable the value of angiography in quantitating narrowing in smaller vessels, particularly when they are downstream of spastic segments. The in vitro studies suggested that diltiazem would inhibit this myogenic activity in the treated monkey.

CHRONIC CEREBROVASOSPASM ARISES FROM CHANGES INITIATED 1–2 DAYS AFTER SUBARACHNOID HEMORRHAGE

The contention that established arterial narrowing is not maintained by continuous active vascular smooth muscle contraction, but by the changes that arise from early arterial damage, implies that this narrowing has its origin in

earlier event(s). One implication of this position is that modification of the earlier event(s) should influence the final state. Evidence relevant to this point is provided by the following three types of observations.

Clot Removal by Suction, Irrigation, or Fibrinolytic Agents

It is very reasonable to hypothesize that if spasm is due to the action of the plethora of vasoactive substances in the clot, the removal of the clot should reduce the seriousness of vasospasm. However, this has not been borne out in practice (30–33). Whether the failure to reduce vasospasm in this way occurs because evacuation is initiated only after surgery and therefore after the damage is done, or because the procedure itself is spasm-provoking, or because the concept is inappropriate is not known. No independent assessment has been made of just how efficacious these procedures are in influencing local concentrations of vasoactive substances in the immediate vicinity of the large arteries at the base of the brain.

A variety of other approaches designed to achieve a similar result by clot lysis or by delaying the formation of fibrin/fibrinogen degradation products have not provided clear-cut evidence of usefulness. In point of fact, antifibrinolytic therapy may have worsened spasm, thus emphasizing the possible importance of certain clot products (34–36).

Anti-Inflammatory Drugs

In the double hemorrhage dog model, pathological changes were seen in the large arteries at the base of the brain at 7 days. Treatment with ibuprofen one hour before and after the initial injection of blood, and continued throughout the study period, reduced meningeal signs and neurological deficit and effected a reduction in angiographic spasm. In vitro, the reduction in basilar artery contraction was smaller in the treated than in the nontreated group. The structural damage that occurred was significantly less in the treated than in the nontreated series (37).

Based upon these animal studies, 21 patients judged to be at high risk for vasospasm were treated with a course of high-dose methylprednisolone, and management results were compared to those for a cohort of matched contemporary control patients. Treatment with methylprednisolone was associated with significant improvement in management outcome, because twice as many treated patients had an excellent result (15 versus 7 patients) and half as many died (3 versus 6 patients) as among the control patients. The incidence and severity of delayed cerebral ischemia was reduced in treated patients in comparison with control patients. None of the treated patients developed a serious side effect that could be attributed to steroid treatment (38). Unfortunately, the series of experiments necessary to prove that the changes

leading to damage originated within the initial period have not been carried out.

The mechanism by which such agents as ibuprofen and methylprednisolone inhibit the vasospasm has not been identified. However, it seems reasonable to conclude that these drugs reduce vasospasm severity by inhibiting the inflammatory response. In this way the integrity of the vascular wall is better preserved.

Evidence From In Vitro Contractions

Toda et al (15) studied the changes that occurred in cerebral arteries after mechanical rupture of the internal carotid arteries of dogs. Narrowing during angiography was shown to be present at 1 and 7 days in the majority of dogs, although details of what changes actually took place and their magnitude are not recorded. At 2 hr, contraction in response to norepinephrine was bilaterally and selectively reduced. Responses to serotonin, histamine, and potassium were unaffected. By the end of the first day, there was, on the side of the hemorrhage, marked depression of contraction in response to norepinephrine and, to a lesser extent, to histamine and serotonin. Surprisingly, the potassium response was somewhat potentiated. At 7 days, the maximum tone developed in response to all agents was decreased, particularly on the side of the lesion. It must be emphasized that these findings are difficult to interpret, since we know nothing about the characteristics of the narrowing at 7 days. However, they do suggest that significant changes consistent with cell dysfunction occur within 24 hr of the hemorrhage.

Effect of Calcium Channel Antagonists

Experiments were undertaken in the monkey to test the idea that the entry of calcium into vascular smooth muscle cells and possibly into endothelial cells is an essential step in the processes that lead to chronic arterial narrowing (29, 39). Pretreatment with diltiazem 48 hr before hemorrhage was initiated not only reduced arterial narrowing during angiography but completely prevented the neurological deficit and remarkably attenuated changes in the artery wall. Before treatment with diltiazem the most constricted standard site on the angiogram had a mean diameter that was 22% of that before hemorrhage. After treatment with diltiazem, this value was 84%—a very significant difference ($p < 0.01$). It must be pointed out that the most constricted site is probably the one of greatest clinical relevance. Although there was a statistically significant narrowing of this site in the diltiazem treated series, the change was relatively small in comparison to the untreated series. The innervation was not protected. The protective value of the diltiazem was much attenuated but was still detectable when its administration was begun 24 hours after hemorrhage (39).

The exact mechanism and site of diltiazem's action in these studies has not been defined. Cerebrovascular smooth muscle is uniquely dependent on extracellular calcium for contraction and diltiazem is cerebrovascularly selective. Thus diltiazem would be expected to reduce calcium entry into cerebrovascular smooth muscle and endothelial cells (40). Presumably, this is the mechanism whereby the vasoconstrictor effects of simple agonists (29) as well as of more complex molecules, such as prostaglandins, blood, and thrombin (41), are antagonized by calcium channel blockers. The reversal by calcium channel blockers of the acute vasoconstriction of cerebral blood vessels by putative spasmogens has been summarized (29). Diltiazem would be expected to prevent calcium overloading and toxic-damage cell death. Whatever the mechanism of the protective effect, these results strongly suggest that only early pharmacological intervention can ameliorate the expected spasm.

Nosko et al (42) examined the possible efficacy of nimodipine in preventing chronic cerebrovasospasm and delayed ischemia after subarachnoid hemorrhage in another monkey model. Spasm was induced by placing autologous hematoma against the major vessels at the base of the brain. The calcium channel antagonist therapy was started 14–20 hr after clot placement and was found not to affect the incidence and severity of chronic cerebrovasospasm. A possible reason for the difference in these two monkey studies is the use of different calcium channel blockers. Diltiazem and nimodipine belong to two different types of chemical compound. Also, the nature of the procedures used to initiate the spasm in the two instances might account for the different conclusions. Parallel data is inadequate to allow further useful comparison.

Some evidence suggests that calcium channel blockers are effective in patients. When prescribed in combination with early surgical treatment (2), nimodipine reduced delayed cerebral ischemic dysfunction in patients with ruptured aneurysms. The same calcium channel antagonist has been shown to have protective efficacy in a selected subset of patients (43). Other calcium channel antagonists seem to be showing value in ongoing clinical assessments.

ACUTE REVERSIBLE CEREBROVASOSPASM

An essential component of our hypothesis is that the seeds of chronic irreversible narrowing of the cerebral artery are sown early, probably within 1–3 days of the hemorrhage. Some evidence suggests that fresh blood causes intense vasoconstriction, which, unlike the chronic phase, is reduced by conventional vasodilator therapy, and that the high concentrations of constrictors occurring at this time are associated with cell damage.

Evidence for Two Phases of Vasoconstriction

The biphasic course of vasospasm described in animal experiments has not been confirmed in humans (2, 44–46). However, an early short-lived transient constriction, perhaps one reversed by radiopaque dye, cannot be excluded. Initial vasoconstriction has been noted in some experimental models (8, 47), and cerebral arterial narrowing has been repeatedly reported after topical application of putative spasmogens. Thus initial early constriction would be expected after subarachnoid hemorrhage. In the study of Varsos et al (48), the narrowing that occurred within 1–3 days of a single injection of blood into the cisterna was pharmacologically reversible. This contrasted with the narrowing found on the fifth day after the second injection, which was not. In one instance, angiography showed bilateral vasoconstriction in the monkey model 24 hr after hemorrhage (J. G. Frazee, personal communication). Its reversibility was not studied. If initial narrowing does occur, it is not associated with neurological defects, as these typically make their clinical appearance on day 4 or later. Just how separate and distinct the two phases of vasoconstriction are; whether the cerebral arteries partly or completely recover their normal diameter after the initial constriction; or whether there is a merging of the early reversible with a later irreversible component, is not precisely known.

Perivascular Vasoactive Material From the Blood Clot: The Artery Wall and Surrounding Tissues

A great deal of evidence indicates that substances released from the clot can directly or indirectly lead to cerebral vasoconstriction. Because of the early breakdown of the blood brain barrier after subarachnoid hemorrhage (49), circulating vasoactive substances have access to the cerebral artery wall. An intrinsic part of our hypothesis is that these products are relevant only to the second phase insofar as they cause initial damage that subsequently develops into chronic narrowing. Only in this sense are short-term in vitro studies of normal vessels relevant to the picture seen 5–7 days after the hemorrhagic insult. There are three aspects to the actions of these substances:

(*a*) Blood products and direct vascular smooth muscle contraction and damage. No attempt will be made to cover this aspect in depth. The extent of spasm is related to the amount of blood in the extracellular space, implying that substances derived from clot are at least major contributors to the problem, although this is not the only explanation of this relationship (50–52). Prevention of clot dissolution has been claimed to prolong and worsen spasm (53, 54). Only when larger needles were used did cerebrovasospasm invariably occur (5).

Many possible spasmogens exist, and these would be expected to be additive in their effect, if not synergistic. They would diffuse directly into the

muscle wall from the adherent clot and influence more distal vessels, probably via the cerebrospinal fluid.

Whether the vascular smooth muscle damage contributing to the chronic state occurs as the result of prolonged and extreme contraction leading to cellular hypoxia, is a consequence of excessive calcium entry and overload, is due to the local generation of toxic substances, or is caused by a combination of these possibilities is a question that cannot now be resolved. Putative spasmogens include epinephrine, norepinephrine, serotonin, angiotensin, hemoglobin, thrombin, plasmin, anti-thrombin III, prostaglandins, thromboxane, hydroperoxide, potassium, fibrin, fibrinogen products, lipid hydroperoxides, and blood and red blood cell products, whether freshly stored or incubated (see 41, 55–70).

(*b*) Blood products and endothelium-based relaxation and damage. A number of clot products are known to release a factor from the endothelium that relaxes vascular smooth muscle (endothelium-derived relaxing factor, or EDRF). EDRF is probably normally released in cerebral arteries by the flow of blood (71) and by the spasmogens that include epinephrine, serotonin, thrombin, and platelets. Hemoglobin and some related products will block this dilator system (72). Endothelial damage and its physical separation from the tunica media will reduce normal flow-induced relaxation. Evidence of early loss of ATP but not acetylcholine-induced endothelium-based relaxation was obtained in rabbits after blood injection into the cisterna magna by Nakagomi et al (73). The change was reversible, and there was no evidence that this model developed chronic cerebrovasospasm.

(*c*) Sympathetic nerve degeneration. After hemorrhage and the subsequent sympathetic storm, adrenergic nerves in both animal and human arteries show loss of catecholamine fluorescence and EM evidence of adrenergic varicosity damage and degeneration (11, 13, 27, 28, 74, 75). This has been confirmed by reduced uptake of tritiated norepinephrine, alteration in transmitter permeability kinetics and attenuation of the vascular smooth muscle response to sympathetic nerve stimulation (10, 74, 76, 77). Loss of adrenergic control would be expected to lead to modest vascular smooth muscle hypersensitivity (78). The vascular smooth muscle cells might be damaged if catecholamine release was precipitous. Damage to nerves, unlike that to vascular smooth muscle and endothelial cells, was not prevented by diltiazem. This may be a common property of calcium channel blockers (79). The basis of neural damage is a matter of speculation.

Reversibility of the Initial Vasoconstriction

Initial vasoconstriction probably depends on physiological constrictor mechanisms. Regulation of vascular resistance in arteries of this size related to normal homeostatic control involves quite modest changes in diameter. High concentrations of vasoactive substances would be expected to occur in

the adventitia after subarachnoid hemorrhage simply because the perivascular nerves, the adherent clot, and ischemic brain tissue are adjacent to the large blood vessel. One hour after a single injection of blood into the cisterna, Varsos et al (48) found a mean reduction of arterial diameter of 18%. Under isotonic conditions, smooth muscle cells are expected to shorten by about 30%; thus such a change in diameter would correspond to 50–70% maximum muscle cell shortening. Mean diameter reduction 48 hr after a single blood injection was 30%, and this was not significantly different from the narrowing that occurred after the second blood injection, and that has features similar to those of chronic vasospasm. The narrowing after one hour was reversed, and that after 3 days greatly reduced by aminophylline.

Reversibility of Contraction Due to Directly Applied Putative Spasmogens

Many putative spasmogens have been applied under direct vision to cerebral arteries exposed during surgery or to strips or segmental preparations of animal and human cerebral arteries in vitro. In a number of instances, it was demonstrated that these contractions were reversed by specific and nonspecific antagonists and by vasodilators, (see 3, for details). The pharmacology of these interactions would in general be expected to be that of high concentrations of agonists and of drugs that modify the agonists' effects. The implication is that putative spasmogens cause contraction of cerebral arteries through relevant physiological mechanisms that are inhibited by conventional pharmacological means.

Evidence That High Concentrations of Spasmogens are Toxic

During sympathetic activity, high concentrations of norepinephrine (in excess of 10^{-4}M) occur at the postsynaptic membrane of the closest smooth muscle cells (78). Excessive norepinephrine release has been implicated as a major causal contributor to the early stages of spasm associated with generalized hyperactivity of the adrenergic system and evidence of local depletion of nerve terminals (see above; 80, 81). Catecholamines in high concentration cause damage of cerebral arteries and other tissues as well (82, 83). That catecholamines are responsible for at least some of the initial events is evidenced by the amelioration seen after reserpine has been administered to the experimental animal (84), although this drug has additional actions, for example, serotonin depletion of platelets (85), mobilization of sequestered calcium from vascular smooth muscle cells (86), and modification of sympathetically induced hypertension. Thrombin has been reported to damage the endothelium (87).

CONCLUSION

Hypotheses about chronic cerebrovasospasm are erected upon fragmentary knowledge gained from clinical experience and from study of a variety of animal models. Some of the latter are more confusing than helpful because they reflect the clinical state with varying levels of authenticity. The necessary and essential criteria for diagnosing chronic cerebrovasospasm are clear beyond all doubt. It is delayed, is essentially unresponsive to vasodilators, and is of sufficient magnitude and distribution to lead to ischemic brain damage or to significantly reduced blood flow. By contrast, the initial vasoconstriction for which evidence in humans is not yet convincing, but which seems quite likely to occur, is immediate and reversible at least transiently by vasodilators. Evidence that cell damage is responsible for irreversibility is supplied by the time course of development, the structural studies, and demonstrated loss of contractility. Supporting this point of view is the relationship between the extent of damage as measured by loss of contractility and angiographic narrowing (10, 29). The precise mechanism of damage has not been defined but is probably multifaceted. Changes in the physical properties of the artery wall can account for chronic narrowing in a monkey model, but in addition, there may be contributing abnormal spontaneous increases in tone. Early processes resulting in damaged arteries have been inhibited by early exposure to the calcium channel blocker diltiazem and also significantly by anti-inflammatory drugs.

Many facets of the proposed picture of the pathogenesis and pathophysiology of spasm are still without scientific verification. However, perhaps for the first time techniques are available that can be used to obtain the missing information.

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