Pathophysiology of Ischemic Stroke

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THRESHOLD CONCEPT OF ISCHEMIC STROKE

The high sensitivity of the brain to a reduction of blood flow is due to the fact that the brain covers its energy demands almost exclusively by oxidation of glucose. A decline of blood oxygen supply below the critical threshold of mitochondrial respiration causes stimulation of anaerobic glycolysis, the energy yield of which, however, is minor as compared to oxidative phosphorylation. Opitz and Schneider (1) were the first to point out that the impairment of oxygen supply to the brain affects the energy consuming processes sequentially: first, the functional activity is impaired, followed—at a more severe degree of hypoxia—by the suppression of the metabolic activity required to maintain structural integrity. By ventilating dogs with declining concentrations of oxygen, they were able to define precisely the two thresholds of functional and structural injury: as soon as the oxygen pressure of cerebrovenous blood fell to below 19 torr EEG reversibly flattened, but when it further declined to below 12 torr, EEG suppression became irreversible and structural damage evolved.

The concept of two different thresholds of hypoxia was later refined by Symon and his coworkers (2) who used a model of acute focal ischemia in the baboon to identify the respective rates of blood flow. The experiments were carried out by combining local blood flow measurements with recording of the EEG and of sensory evoked potentials for assessing the electrical function of the brain, and with recordings of extracellular potassium activity for evaluating the maintenance of intra/extracellular ion homeostasis and, hence, cell integrity. By placing their electrodes at different parts of the cortical territory of the occluded artery, they noted that the amplitude of evoked potentials and of spontaneous EEG activity collapsed at flow values below 0.15 ml/g/min or 30% of control, whereas extracellular potassium activity remained undisturbed unless blood flow further declined below 0.10 ml/g/min or 20% of control (3). At this threshold, extracellular potassium rose sharply, indicating the sudden depolarization of cell membranes. In the normothermic mammalian brain, maintenance of transmembrane ion gradients is an active energy-consuming process and therefore a sign of cell viability. The demonstration of two flow
thresholds, a higher one leading to "electrical failure" and a substantially lower one associated with "membrane failure" suggest that in the flow range between these two thresholds, cerebral cortex is functionally silent but structurally intact. In focal ischemia, this flow range corresponds to a circular region intercalated between the necrotic infarct core and the normally perfused brain tissue. This region has been termed penumbra in analogy to the partly illuminated area around the complete shadow of the moon in full eclipse (4).

When the penumbra concept of ischemic injury evolved, it was acclaimed with great enthusiasm because it evoked the hopes that the functionally silent peripheral parts of the ischemic territory could be reactivated by raising blood flow above the critical threshold of functional impairment. Great efforts have therefore been made to improve blood supply to the ischemic penumbra by using vasodilating agents, by lowering the viscosity of the circulating blood or by reconstructive surgery. However, when rigorously tested in comparison to the spontaneous resolution of neurologic symptoms, most of these interventions failed to improve the functional deficits significantly (5).

On the other hand, compelling evidence has accumulated over the past years that ischemic injury can be substantially reduced by means other than flow improvement. Various drugs that interfere with signal transduction pathways, notably glutamate antagonists, can substantially reduce the size of ischemic infarcts, although blood flow is not or only marginally altered (6). The concept of ischemic thresholds has, therefore, become much more complex and has to consider secondary responses which are indirectly linked to the primary disturbance of blood flow.

METABOLIC AND FUNCTIONAL THRESHOLDS OF CEREBRAL ISCHEMIA

During the initial few hours of focal cerebral ischemia, different brain functions break down at widely varying flow levels (Fig. 1). Progressing from the periphery to the core of the infarct, the most sensitive index is protein synthesis. In gerbils and rats, protein synthesis begins to decline at values that are close to normal (7–10). According to Mies et al. (9), protein synthesis is inhibited in rats by 50% at about 0.55 ml/g/min, and it is completely suppressed below 0.35 ml/g/min. These values are clearly above the threshold of mRNA synthesis which begins to decline below 0.25–0.35 ml/g/min (11). At this level also, changes of glucose utilization are present: in small rodents, it transiently increases at a flow rate below 0.35 ml/g/min before it sharply declines below 0.25 ml/g/min (12). The upper level of glucose activation corresponds to the beginning acidosis and the beginning accumulation of lactate (13–17). At flow rates below 0.26 ml/g/min, tissue acidosis becomes very pronounced (15) and both phosphocreatine and ATP begin to decline (9,12–17). Naritomi et al. (14) reported a slightly higher threshold for the depletion of phosphocreatine (0.18–0.23 ml/g/min) than that for ATP (0.13–0.14 ml/g/min) which is in
line with the faster phosphocreatine decline under conditions of complete ischemia (18).

Anoxic depolarization, as assessed by recording extracellular potassium (3,19–21) and calcium activities (21,22), or by measuring the tissue contents of sodium and potassium (23,24), occurs at even lower flow values. The sodium/potassium ratio of brain tissue increases at flow values below 0.10–0.15 ml/g/min (23), and the extracellular ion changes occur between 0.06 and 0.15 ml/g/min (3,19–21). At the same threshold, extracellular calcium declines due to the opening of calcium channels (21,22). The metabolic and ionic disturbances in the periphery of focal ischemia thus proceed in the following order: initially protein synthesis is inhibited (at a threshold of about 0.55 ml/g/min), followed by the suppression of mRNA synthesis and a stimulation of anaerobic glycolysis (below 0.35 ml/g/min), the breakdown of energy state (at about 0.20 ml/g/min) and anoxic depolarization of the cell membranes (below 0.15 ml/g/min).

As far as the functional disturbances are concerned, the first change is the slowing
of EEG activity, followed by amplitude reduction of EEG and evoked potentials. Complete suppression of EEG activity occurs between 0.15 and 0.23 ml/g/min (4,14,20,25); evoked potentials disappear between 0.15 and 0.25 ml/g/min (3,20,26,27) and spontaneous unit activity at a mean value of 0.18 ml/g/min (28,29). The latter, however, greatly varies in different neurons between 0.06 and 0.22 ml/g/min. Neurological studies suggest that reversible hemiparalysis appears in monkeys at about 0.23 ml/g/min, followed by irreversible paralysis below 0.17-0.18 (20,30). All these values are distinctly below the threshold of the suppression of protein synthesis and even below that of the beginning of activation of anaerobic glycolysis but they fall into the range of the beginning of energy crisis, indicating that functional suppression is, in the first place, the result of energy failure.

This is also true for the release of neurotransmitters into the extracellular compartment, as measured by interstitial dialysis techniques. In cats and rats, both inhibitory and excitatory neurotransmitters are released at a flow rate below 0.2 ml/g/min with a possibly slightly higher threshold for glycine, adenosine, and γ-aminobutyric acid (GABA) than for glutamate (27,31–35). Dopamine and serotonin release has been measured in a graded global ischemia model of rat and was found to increase transiently at flow values below 21–48% of control before it permanently increased at a flow rate below 14% (36). The release of neurotransmitters is probably nonspecific because other intracellular metabolites are co-released (37,38).

A direct consequence of the metabolic disturbances associated with focal ischemia is the rise of cell osmolality which causes a shift of water from the extracellular into the intracellular compartment (39). The resulting decline in the fluid volume of the extracellular space can be detected by measurements of electrical impedance (23,24,40) or by diffusion-weighted nuclear magnetic resonance (NMR) imaging (16,17,41–44), both of which are sensitive to cell volume changes. Two hours after vascular occlusion, the threshold for the beginning rise of electrical impedance in cats is about 0.3 ml/g/min (40) and that of the rise of signal intensity in diffusion-weighted imaging measured in rats is 0.41 ml/g/min (16). These thresholds are distinctly higher than the threshold of brain edema—defined as the volumetric increase of water content—which is close to 0.1 ml/g/min (23) and which corresponds to that of anoxic cell membrane depolarization. This difference is the reason for the fact that T2-weighted NMR imaging, which detects alterations of tissue water content, is less sensitive to ischemic changes than diffusion-weighted imaging (41).

In contrast to the biochemical and functional changes which appear shortly after vascular occlusion, histological lesions require some time before they become visible. The threshold of histological changes therefore depends on both the density and the duration of the flow reduction as described in more detail next. Under conditions of permanent focal ischemia, the threshold of pan-necrosis is between 0.17 and 0.24 ml/g/min (30,45). At flow values below 0.80 ml/g/min, that is, far above the threshold of pan-necrosis, selective neuronal loss may occur (46). Interestingly, this loss is not threshold-dependent: the flow rate correlates linearly with the number of surviving neurons, which suggests a coupled decrease in parallel with the reduced metabolic requirements of the tissue. This interpretation is in line with the hypothesis that the
peri-infarct brain tissue suffers pathological changes which are not necessarily caused by a critical reduction of blood flow.

DIFFERENTIATION BETWEEN CORE AND PENUMBRA OF ISCHEMIC STROKE

According to the threshold concept of ischemic stroke, brain tissue is functionally impaired but remains structurally intact as long as blood flow lingers between the thresholds of electrical and membrane failure. For clinical purposes, imaging of the penumbra is of considerable importance because it is this part of the ischemic territory which can be expected to profit from therapeutic interventions. A straightforward way to image the penumbra is the identification of the thresholds of functional and structural integrity by regional measurements of blood flow. In the baboon, these thresholds are 0.15 and 0.10 ml/g/min or 30% and 20% of control, respectively. In humans, structural damage occurs when blood flow declines below 0.12 ml/g/min and oxygen utilization below 0.65 μmol/g/min (47,48). Although these thresholds are widely cited, they are, in the strict sense, only valid for the particular situations under which they were measured, that is, in awake humans and in the lightly anesthetized baboon. In fact, the thresholds of functional and structural integrity differ in species with different neuronal densities, and in the same species, they change with the anesthesia or the duration of ischemia. Efforts have therefore been undertaken to identify the penumbra by other criteria which are independent of the species or the duration of ischemia.

Selman et al. (49) proposed staining tissue sections with neutral red to identify the areas of acidosis, because acidosis is a characteristic feature of impeding ischemic injury. Another way for imaging the regions of acidosis is the in vivo or in vitro umbelliferone technique (16,17,50,51). De Graba et al. (52) advocated the use of calmodulin staining because the loss of staining indicates increased intracellular calcium uptake, which in turn is thought to initiate the pathological process leading to cell death. Another approach is imaging of the inhibition of protein synthesis because the threshold of amino acid incorporation is higher than that of ATP depletion (9). Finally, attempts have been made to identify the penumbra by visualizing the expression of immediate early or heat shock proteins (53–55), by labelling activated calcium channels with nimodipine (56) or by application of nitroimidazoles as hypoxic cell markers (57).

A widely used approach for the noninvasive localization of the penumbra is the measurement of oxygen extraction fraction using positron emission tomography (58). Under conditions of reduced blood flow, oxygen extraction from the circulating blood increases, provided the oxygen consumption does not change. As soon as metabolism ceases, even the residual supply of oxygen will not be used and the oxygen extraction fraction declines. A problem of this approach is the uncertainty about the coupling between oxygen utilization and oxidative phosphorylation which may suffer during ischemia because the increased cytosolic calcium load reduces
the oxidative capacity of the mitochondria (59). There are also methodological limitations because the oxygen extraction fraction is the quotient of oxygen consumption divided by oxygen supply and has to be calculated from two independent measurements—blood flow and oxygen utilization. At low flow values, both variables approach zero and the quotient becomes very sensitive to spurious fluctuations of background activity. This leads to poor statistics and, in consequence, a further reduction of the already limited regional resolution of positron emission tomography.

An alternative technique for noninvasive visualization of the penumbra is diffusion-weighted magnetic resonance imaging (DWI) (16,17). The signal intensity of this imaging modality is the function of water compartmentation (41) which, in turn, depends on intracellular/extracellular osmolar and ion homeostasis (39,40). During ischemia, water is shifted from the extracellular to the intracellular compartment, leading to a restriction of tissue water diffusion (42). In DWI, this decline results in an increase in signal intensity which can be detected within a few minutes after vascular occlusion (16,41,60). Combining DWI with regional flow measurements or pictorial assays of brain metabolites revealed that the outer border of the DWI-visible region corresponds to that of tissue acidosis (16). During the early stages of infarct evolution, this region is distinctly larger than that of ATP depletion, indicating that DWI visualizes both the core and the penumbra.

The problem of this and other imaging methods is the uncertainty about the precise demarcation of the penumbra from either the normal or the necrotic tissue. A demarcation against the necrotic tissue is not possible because most of the penumbral disturbances—suppression of electrical activity, acidosis, calcium accumulation, inhibition of protein synthesis, and oxygen utilization—also affect the ischemic core. As far as the demarcation of the penumbra against the normal tissue is concerned, a conceptional problem arises because the peripheral borders of the functional disturbances may not be congruent. For example, tissue acidosis or the reduction of water diffusion are confined to the area in which anaerobic glucose utilization is stimulated, whereas other functional abnormalities such as the expression of immediate-early or heat shock proteins may include the whole ipsilateral hemisphere. To overcome this problem, we defined the penumbra as the region of reduced blood flow in which energy metabolism is preserved (Fig. 2) (61). This definition considers the fact that ischemia is a reduction of blood flow and that energy metabolism is required to maintain structural integrity of the tissue. According to this definition, the outer border of penumbra corresponds to the border of declining blood flow and the inner border to the transition zone between high and low ATP content. The advantage of this definition is the possibility of identifying these borders by invasive or noninvasive imaging techniques, irrespective of the species or the particular experimental method. However, this definition ignores the fact that alterations outside the area of reduced blood flow, in particular, the widespread genomic abnormalities, may also be of pathognomic importance for the evolution of brain infarcts.

**TEMPORAL EVOLUTION OF ISCHEMIC STROKE**

Multiparametric imaging of the developing infarct of rat after permanent occlusion of the middle cerebral artery revealed that the core region of the infarct gradually
FIG. 2. Imaging of core and penumbra of evolving infarct following middle cerebral artery occlusion in rat. Measurement of cerebral blood flow by \( ^{14}C \)iodoantipyrine; ATP content, by substrate-induced bioluminescence; and tissue pH with umbelliferone. The core of infarct is the central region in which ATP is depleted (as reflected by loss of ATP bioluminescence), and the penumbra is the region of reduced cerebral blood flow in which ATP is preserved. Note that tissue acidosis includes both the core and the penumbra of infarct. Sections are from three different experiments with different sizes of core and penumbra.

expands into the peri-infarct penumbra zone (9,16). After a 30-minute vascular occlusion, the outer margin of the penumbra visualized by diffusion-weighted imaging encompasses a region that is more than twice as large as that in which ATP is depleted (16). After 2 hours, this ratio declines to 1.4, and after 7 hours, the DWI-visible and ATP-depleted regions are congruent (44). At this time, the penumbra has disappeared and is now part of the irreversibly damaged infarct core. Blood flow remains stable during the initial hours of ischemia which excludes the possibility that the growth of the infarct core is due to a progression of ischemia.

An important factor contributing to the expansion of tissue injury into the penumbra zone is possibly the occurrence of spreading peri-infarct depression (depolarizations) (Fig. 3). As first described by Nedergaard and Astrup (62), such depolarizations are generated by the infarct core from where they spread into the peripheral zone. During spreading depression, the metabolic rate of the tissue markedly increases in response to the greatly enhanced energy demands of the activated ion exchange pumps (63,64). In the healthy brain, the associated increase of glucose and oxygen demands are coupled to a parallel increase of blood flow, which may rise to more than 200% of control (63,65,66). This flow response is suppressed in
FIG. 3. Peri-infarct depolarizations in the surrounding of ischemic infarct after middle cerebral artery occlusion in rat. Recording of electroencephalogram (EEG) and cortical steady potential (DC). Depolarizations correspond to negative DC deflections and are associated with transient inhibition of EEG activity.

the peri-infarct penumbra because the reduced hemodynamic capacity of the collateral system prevents the adequate coupling of blood supply to the metabolic needs of the tissue (67). As a result, a misrelationship arises between the increased metabolic workload and the low oxygen supply. In fact, recordings of tissue oxygen pressure during KCl-induced spreading depression in intact animals and during peri-infarct depolarizations in middle cerebral artery occluded rats clearly show that the latter result in transient episodes of tissue hypoxia during the passage of each depolarization (68). Evidence of tissue hypoxia has also been provided by biochemical and NMR spectroscopic studies which revealed substantial increase of lactate in the area of peri-infarct depolarizations (69-71).

The pathogenic importance of peri-infarct depolarizations for the progression of ischemic injury is supported by the close linear correlation between the number of depolarizations and infarct volume (72,73). Correlation analysis of this relationship suggests that during the initial 3 hours of vascular occlusion, each depolarization increases the infarct volume by more than 20%. This is the reason why pharmacological suppression of peri-infarct depolarizations by competitive and noncompetitive glutamate antagonists reduces the volume of brain infarcts (73-75). Using NMR spectroscopic and tomographic recordings, the close temporal correlation between peri-infarct depolarizations and enhancement of the ischemic injury could be confirmed by demonstrating sudden increases in the concentration of lactate and the volume of the DWI-visible brain region immediately after such transients (70).

It has been argued that spreading depression may be of limited importance for the expansion of the ischemic infarct because even two hours of repeated depolarizations in moderately hypoglycemic rats did not produce neuronal damage, although the constrained glucose supply led to a marked prolongation of the calcium transients (76). However, this observation does not invalidate the present hypothesis. The infarct core expands with each spreading depression only by a finite amount, although the depolarizations spread over the entire hemisphere. This suggests that the
ISCHEMIC STROKE

aggravating effect is manifested in the immediate vicinity of the ischemic core, that is, in the region in which oxygen supply is closest to the threshold of anoxic depolarization. The cumulation of the ischemic injury by repetitive depolarizations can therefore readily be explained by the conversion, in the infarct border zone, of a transient into a terminal depolarization (77).

Spreading depolarizations may also be responsible for the selective neuronal loss observed in the more peripheral surrounding of the ischemic infarct (78). This hypothesis is supported by threshold determinations of protein synthesis following pharmacological suppression of peri-infarct spreading depressions with glutamate antagonists. This treatment led to a remarkable lowering of the threshold of protein synthesis from 0.51 to 0.19 ml/g/min, which comes close to that of energy failure (79). This observation suggests that peri-infarct spreading depression may not only be responsible for the expansion of the infarct core but also for the widespread inhibition of protein synthesis that could lead to peri-infarct disseminated neuronal loss.

An argument against the aggravating role of spreading depression is the possibility that the frequency of peri-infarct depolarization depends on the volume of the ischemic core and not the other way around. Pharmacological interventions that are able to reduce the ischemic impact could therefore also result in a reduction of the number of peri-infarct depolarizations. Although this argument cannot readily be refuted, it does not invalidate the conclusion that injury in the periphery of the ischemic infarct is not solely a function of the rate of blood flow. Therefore, an understanding of the pathophysiology of focal ischemia has to take into account not only the reduction of blood supply and the associated metabolic disturbances, but also the state of functional activation.

CONCLUSION

Analysis of the functional and biochemical alterations of focal ischemia shows that the resulting brain infarct is not just a demarcated volume of necrotic tissue but a region of highly complex pathological processes which gradually progress and result in the aggravation of tissue injury. It is suggested that an important factor for these pathological processes is the repetition of spreading depression-like depolarizations. The most straightforward way for salvaging the penumbra is therefore the suppression of these depolarizations. Glutamate antagonists are highly efficient at achieving this but it is reasonable to assume that less toxic drugs which are also able to suppress spreading depression or the metabolic workload associated with this complication may have the same effect. If this hypothesis is confirmed, research on stroke therapy may take a new direction.

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26 ISCHEMIC STROKE


DISCUSSION

Dr. Kahn: I have a question concerning glutamate receptor antagonism. These receptors are on both the neuronal and the glial cells. Do you have any idea whether the glial cells are involved and how this interaction of glial cells and neuronal cells works?

Dr. Hossmann: The depolarization is not only in the neurons; the glial cells are also depolarized which means that there is also a substantial stress on the ion homeostasis of the glial cells. I therefore would predict that a substantial part of the work load is on the glial cells.

Dr. Guesry: You showed in your rat experiments that you could break the vicious circle by using a glutamate receptor antagonist, but have you tried modifying the osmolality or buffering the pH modification, which could also play an important role in this increase in infarct size? Taurine was cited decades ago as an important osmotic factor in brain cells. Have you any experience of that?

Dr. Hossmann: We have done some work in measuring tissue osmolality under ischemic conditions and we found that osmolality in the ischemic tissue increases, beginning at a higher threshold than that of ATP depletion; in other words, the osmolality begins to increase before the ATP is depleted. The increased osmolality can be associated with increased lactate, breakdown of energy metabolites and, of course, also the uptake of cations. It is the final reason for the shift of water which I have shown, and there is a very close correlation between osmolality of the tissue and the size of the extracellular space. So, the increased osmolality is certainly a very important pathophysiological factor for causing what we see in diffusion-weighted magnetic resonance imaging. Whether this contributes to the tissue injury is questionable, because we know that after complete global ischemia of up to 1 hour the increased osmolality is fully reversed. I, therefore, believe that the increased osmolality is an accompaniment of the pathological process and not the reason for the injury, unless the uptake of fluid is such that it causes a major increase in intracranial pressure.

Dr. Kornhuber: When I read the literature about glutamate antagonists, I find that if you use them in an animal model in therapeutic doses, you will completely block those centers in the pons which control breathing; thus in clinical practice, we would have a situation where we would first have to refer the patient to an ICU and then start therapy; we would lose at least an hour or so before we could start treatment. Do you think this could be advocated?
Dr. Hossmann: Not if the beginning of the therapy is delayed. But there may be other drugs which suppress spreading depression, giving time for the preparations necessary to induce thrombolysis or other interventions for improving blood flow to the endangered area.

Dr. Kornhuber: Since the spreading depression concept is so attractive, one question is whether in fact it occurs in man. There is some hint that it does. On the other hand, from the topography of your lesions in the animal and the time of the spreading depression, is there any evidence that this changes after the occlusion? In other words, is the depression more vigorous or more extended immediately after the occlusion, and does it then decline? Is there anything to suggest that this is a dynamic process? I also had the impression that the spreading depression was perhaps more marked in the cortical than in the subcortical regions.

Dr. Hossmann: The depression extends over the whole hemisphere, both cortical and subcortical. I cannot say how vigorous the process is, but once it is evoked, it spreads over the whole hemisphere, though the frequency of spreading depressions varies greatly. I have the impression that the rate of spreading depressions declines somewhat with time, and it is possible that after a couple of days, they will completely cease.

Dr. Stähelin: I would like to come back to the question of the fluid shift into the cell. Could you measure in your system whether the change in size of the cell actually induces the different gene expression? It has been shown that if you increase the size of liver cells, it profoundly affects gene expression (1).

Dr. Hossmann: This would agree with our finding that c-FOS is induced in the whole hemisphere, even far away from the ischemic territory. In fact, it is known from work by Herdegen et al. (2) that spreading depression in the intact animal induces various transcription factor proteins such as JUN, FOS, KROX, and CREB which suggests that expression of c-FOS in focal ischemia is due to peri-infarct depolarizations. Spreading depression also induces widespread activations of astroglia (3) or microglia (4) which suggests that this may also be a mechanism for the glial activation around focal ischemia. But one must be cautious not to relate everything to the spreading depression. HSP70 expression, for instance, is strictly localized in the penumbra which means that it must be related to metabolic disturbances occurring only in this region. The spreading depression may be a triggering event but the manifestation of the stress response must be a combination of this and other ischemia-related events.

Dr. Elmadfa: In your experimental model, do you have evidence of an inflammatory response or cellular infiltration during the evolution of the infarct?

Dr. Hossmann: We did not look at that but it is known that there is a widespread inflammatory response. The question is whether it is of pathological importance for the kind of permanent occlusion which I showed. I suspect that the inflammatory response may be of greater pathophysiological significance under conditions of spontaneous reperfusion.

Dr. Bogousslavsky: You mentioned that glutamate antagonists may have different modes of action. In your model, how can you be sure that the beneficial effect of these agents is derived from their effect on depolarization?

Dr. Hossmann: By inference; because we know from in vitro studies that the neurons are quite resistant to glutamate. The concept of glutamate excitotoxicity is based on in vitro work which is done under very special conditions. If you adjust the incubation conditions closer to the in vivo situation—e.g., by adding trophic factors to the culture medium—glutamate is much less toxic. Also, if you take the step from cell culture to slice, you will find that it is not possible to damage neurons with glutamate at all. There is, in fact, little evidence that ischemic injury, be it global or focal, is mediated by glutamate toxicity in the true sense, that
means by neuronal intoxication. There must be some kind of functional load on the tissue which leads to injury, not the glutamate itself.

Dr. Feller: Are you aware of any interactions between glutamate antagonist and calcium channel blockers?

Dr. Hossmann: As you know, the NMDA type glutamate-operated ion channels have a calcium conductivity and the activation of this channel causes a cellular calcium flooding. Ischemia causes calcium influx also across voltage-operated calcium channels. The question is, if ischemia-induced calcium flooding is detrimental, and most of the evidence is that it is not. When the brain is recirculated with blood, energy metabolism is restored, cell membranes repolarize, calcium is pumped out and the tissue recovers. This may be the reason that the therapeutical effect of calcium antagonists is greatly disputed.

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