BIOCHEMISTRY OF MIGRAINE

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INTRODUCTION

Migraine can be defined as a familial disorder of unknown etiology, characterized by recurrent attacks of headache, commonly unilateral and variable in intensity, frequency and duration. Data on the frequency of migraine in the general population are conflicting.

Disturbance of cerebral blood vessels seems to be important in the pathogenesis of migraine. Initially the aura or prodromal phase occurs associated with vasoconstriction of intracerebral arteries leading to cerebral ischaemia and resulting in cerebral malfunction, such as hand numbness or disorder of vision. This is succeeded by vasodilatation of extracerebral arteries causing headache and tenderness (1). Vacoactive compounds seem to be very important in provoking a migraine attack. 5—hydroxytryptamine (5—HT, serotonin) is one of the vasoactive compounds.

5—HYDROXYTRYPTAMINE

Although the platelets contain about 99 % of the blood 5—HT they cannot synthesize 5—HT due to the lack of enzymes necessary for synthesis. However they can catabolize 5—HT. It is actively taken up by platelets and released when the platelets aggregate. 5—HT is also released in response to various stimuli such as catecholamines (2).

Since platelets have been considered to be possibly related to the pathogenesis of migraine, they have been extensively studied. Sicuteri et al. (3) first suggested a role for 5—HT in the physiopathology of migraine. They observed alterations in plasma 5—HT of migraine patients and they reported an increase in urinary excretion of 5—hydroxyindoleacetic acid, a breakdown product of 5—HT, during migraine attacks. Increase of 5—HT during migraine attacks has also been shown by other investigators (4—6). In 1979 Mück—Seller et al. (7) found that the mean platelet concentration of 5—HT in non—migraine subjects was similar to that of migraine sufferers during a headache—free period, but during a migraine attack a significant decrease in platelet 5—HT occured. They have suggested that there is a platelet abnormality in some migraine sufferers and during a migraine attack a 5—HT releasing factor is present.

The release of 5—HT from platelets increases plasma 5—HT. The release of histamin and proteolytic enzymes from mast cells are also postulated to occur during the prodromal phase (8). High plasma levels of 5—HT cause a profound vasoconstriction and a decrease in cerebral blood flow, which may give rise to prodromal symptoms (9). The presence of free 5—HT and histamine cause a marked increase in capillary permeability. This allows transudation of 5—HT as well as free plasma kinins into the vessel wall, thus lowering the local pain threshold (8,10). At this point , 5-HT is rapidly taken up by the platelets and the spleen and rapidly excreted by the kidneys. The net effect is a precipitous fall in plasma 5—HT levels (8,11). In an environment of relative 5—HT depletion the involved vessels dilate and passively distend, resulting in the classic pulsatile headache. Sterile inflammation develops in perivascular tissue and nerve endings around the vessel wall become sensitive (8,10). 5—HT appears to function as an inhibitory neurotransmitter for some brain stem neurons associated with the perception and integration of pain. These neurons are within the raphe nuclei (12).A relative deficiency of central 5—HT, which has been demonstrated in migrainours, would lead to a disinhibition of these central pain centers, manifesting as hyperalgesia to afferent pain impulses (13,14). The 5—HT lowering in migraine leads to hypersensitivity of the vomiting centre in the medulla oblongata, perhaps explaining the nausea frequently experienced in migraine. Furthermore interruption of aminergic neuronal pathways in the hypothalamus is thought to be responsible for the mood changes observed in migraine. Lowered brain 5—HT has been shown in experimental animals to give rise to irritability and indeed, irritability is often seen in the initial stage of a migraine attack. Bright light and stress are capable of reducing brain 5—HT levels, it is interesting that both are documented triggerers of migraine. Migraine sufferers could conceivably experience widely fluctuating 5—HT levels in the peripheral compartment while exhibiting chronically low 5—HT levels in the central compartment since 5—HT does not readily transverse the blood brain barrier (13). 5—HT may act also upon the carotid body via a chemoreceptor and hence influence vascular calibre indirectly (15). On the other hand, transient blood brain barrier damage has been reported in migraine (16).

Why do platelets lose their ability to retain 5—HT at the beginning of a migraine attack? As previously mentioned it has been supposed that the decrease in platelet 5—HT concentration is caused by the presence of a platelet 5—HT releasing factor(s), which appear in the blood during the attack

(7,17,18) and the platelet release reaction occurs while the migraine attacks develop (19).

There is evidence that changes in bulk lipid fluidity of the platelet membrane affect its aggregation. In migraine lipid fluidity has been reported to be increased (20,21). The content of phosphatidylcholine, the amount of arachidonic acid in phosphatidylcholine and the amount of unsaturated fatty acids in phospholipids of platelet membrane are found to be increased in migraine patients. Therefore it is suggested that platelet membrane lipid composition may play a role in the frequency and severity of migraine attack (22).

TYRAMINE

Another vasoactive amine which is important in migraine is tyramine. Tyramine occurs in the body partly as the result of endogenous synthesis by decarboxylation of tyrosine and partly from the diet. Tyramine itself is a vasoactive amine and it can be directly responsible for the initial vasoconstriction in migraine. Furthermore tyramine can displace 5—HT from storage sites in platelets and therefore it may be one of the 5—HT releasing factors. Now it has been known that tyramine rich foods such as cheese and citrus fruits are migraine triggerers. What is the reason that tyramine can induce migraine in migraine sufferers but not in control subjects? There is evidence of defective tyramine metabolism in some migraine sufferers possibly enabling tyramine of dietary origin to remain longer in the circulation. About 15 % of ingested tyramine is converted into tyramine—0—sulphate in normal subjects but tyramine—sensitive migraine sufferers excrete significantly lower amounts (23—25).

MONOAMINOXIDASE

Monoamine oxidase (MAO) is one of the principal enzymes involved in the metabolism of monoamines such as 5—HT, tyramine, phenylethylamine, and catecholamines by the process of oxidative deamination. On electrophoresis basically two forms of MAO are observed; MAO—A, which prefers 5—HT as substrate and MAO—B which prefers phenylethylamine. Both isoenzymes can metabolize tyramine and noradrenaline. A deficiency in platelet MAO—B during migraine attack has been observed. This can lead to defective inactivation of vasoactive amines and could cause local accumulation of amines, perhaps in the lungs, with subsequent release into the systemic circulation and eventually the cerebral circulation (26—30).

CATECHOLAMINES

Increased sympathetic activity and altered catecholamine metabolism has been described in migraine. Increased excretion of 4—hydroxy—3—methoxy—mandelic acid (4), lowered MAO activity in platelets (26—30) and elevated plasma noradrenaline concentrations are reported during migraine headache (31). Noradrenaline is a vasoactive amine and may exert an effect upon the cerebral vasculature which is important in the pathogenesis of migraine. Also, noradrenaline is capable of causing platelet aggregation and 5—HT release consequences of which are described above. Serum dopamine —β— hydroxylase (DβH) concentration has been reported to be an indirect measure of peripheral sympathetic activity (32). It is considered to be more reliable index than the concentration of noradrenaline, since noradrenaline is rapidly inactivated by pre—and post—junctional uptake (33). DβH, the final enzyme in the biosynthesis of noradrenaline is localized in the noradrenaline—storage granules at the sympathetic nerve endings innervating blood vessels and upon sympathetic stimulation it is released by exocytosis in quantities proportional to the amount of noradrenaline released. The enzyme has been reported to be increased in the serum of migraine patients (34,35). It has been suggested that the elevation of DβH may be the result of either primary involvement of noradrenaline in the pathogenesis of migraine or heritable instability of the vascular system in migraine sufferers. The fact that stress is not only an important precipitating factor of migraine attacks but is also associated with elevated plasma catecholamine concentrations, especially noradrenaline, adds support to the concept of abnormal sympathetic control in migraine (36,37).

PROSTAGLANDINS

It has been reported that platelet adhesivenes and aggregation is increased during the intervals and prodromal phases of migraine (2,38). Thromboxane A_2 (TXA_2),(the main metabolite of arachidonic acid in platelets) is formed by thromboxane synthetase and prostacyclin is formed by prostacyclin synthetase in the vascular endothelial tissue and white blood cells. The local balance between TXA_2 and prostacyclin is the important determinant of platelet aggregability. TXA_2 is a potent platelet aggregant and vasoconstrictor and it stimulates 5—HT release from platelets. Prostacyclin, on the other hand, is a potent inhibitor of platelet aggregation and a vasodilatator. Inhibitors of prostaglandin synthesis, especially thromboxane synthetase are found to be effective in the treatment of migraine (39—41). These results support the role of the metabolites of arachidonic acid in the pathogenesis of migraine. In addition, during the headache—free period in migraine, decreased platelet TXA_2 formation is observed and it may be due to an increased consumption of arachidonic acid in the platelets during migraine attacks (42).

FATTY ACIDS

Some fatty acids have been shown to act as "platelet 5—HT releasing factors". Long chain, saturated fatty acids such as stearate, linoleate, linolenate and oleate can promote the liberation and subsequent metabolism of arachidonic acid in blood platelets (43). Products of this metabolism (TXA_2,PGG_2,PGH_2) can induce aggregation and release of 5—HT from blood

platelets (43,44). A remarkable correlation between the rise of free fatty acids and hyperaggregability of the platelets during migraine episodes have been observed (45,46).

CHOLESTEROL

Cholesterol also has been found to have a proaggregatory effect on the blood platelets (47,48). Cholesterol stimulates the activity of platelet cyclo—oxygenase and then cyclic prostaglandin endoperoxides (PGG_2, PGH_2) and TXA_2 are synthetized. These substances stimulate platelet aggregation and release (49). The level of total blood cholesterol has shown a heterogenous distribution in migrainours. In some of the migrainours having lower platelet aggregation during headache—free intervals, high cholesterol levels have been found. Therefore the total blood cholesterol is suggested to be one of the factors which define a portion of migraine population (46).

OTHERS

Certain factors clearly precipitate migraine attacks in susceptible patients, but their clinical importance is the subject of much debate (50—52). Many patients have no identifiable precipitating factors and these patients often report inconsistent responses. Some of the more common precipitating factors are food, fasting, light, sleep and fever. The foodmost commonly cited as triggering agents are presented in descending rate of frequency: chocolate, alcohol, cheese, monosodium glutamate, nuts, citrus fruit, meat, coffee, nitrates, fish, dairy products, onions, hot dogs, pizza, wheat products, banana, tomatoe, apple, and various vegetables. Fasting or ingestion of chocolate, cheese, alcohol produce a sharp rise in plasma free fatty acid levels. High circulating levels of free fatty acids can release 5-HT from platelets. On the other hand, some of the foods include tyramine, phenylethylamine and allergic factors (53).

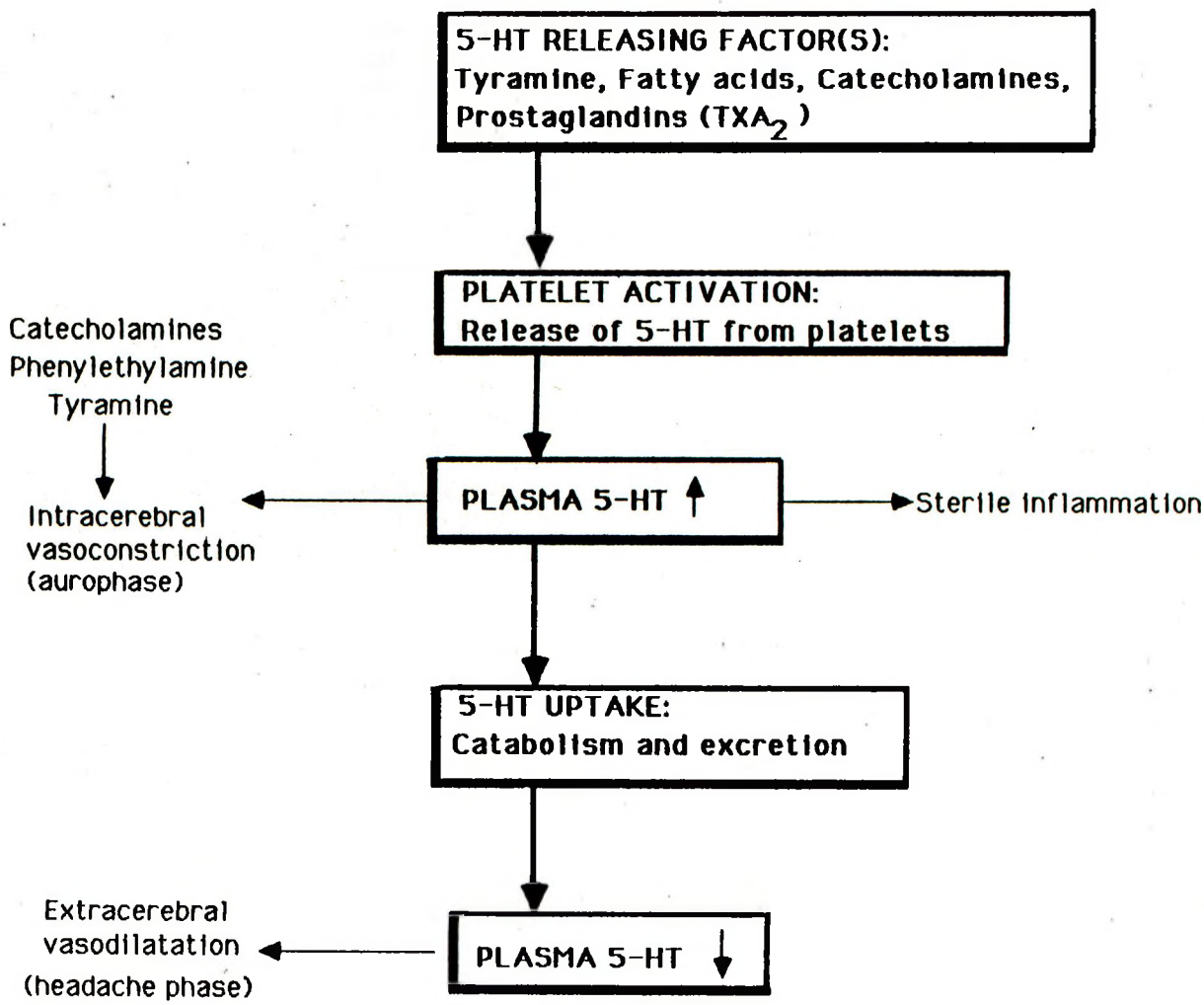

Fig 1. Summary of biochemical events proposed to occur in the migraine process

Recently, attention has been focused on the biological effects of other arachidonic acid metabolites, particularly of those involved in lipoxygenase pathways, such as leukotrienes. It is also shown that the leukotrienes are present in the central nervous system and some evidence has been provided of a neuroendocrine role of leukotriene C_4 in rat brain (54,55). Although the role of lipoxygenase pathway metabolites in the pathogenesis of migraine is not yet well established, some recent reports point to potential involvement of leukotriene D_4 in the regulation of intracranial blood flow (56). It is also an interesting finding that increased amounts of leukotriene B_4 was obtained during the prodromal phase. Greater amounts of leukotriene C_4 was obtained at the beginning of the attack phase. In other words the onset of migraine attack is initially accompanied by the presence of leukotriene B_4 in blood and subsequently by the appearance of leukotriene C_4. Leukotriene B_4 is mainly released from leucocytes. There fore it is suggested that the lipoxygenase metabolites may result from an extraplatelet origin and leukotrienes play a role in the regulation of platelet response to aggregation inducers (57).

CONCLUSION

In summary, migraine is a disorder that recurs at intervals. Platelets show a gradual increase in potential 5—HT release between attacks and an attack can only occur when certain factors reach a critical level (Fig. 1). When this significant increase in 5—HT release takes place, it appears to trigger the complex chain of vascular responses and biochemical events that characterize the migraine attack. For the time being the biochemical and physiological events that initiate and perpetuate the migraine headache remain poorly understood. Therefore many people suffer from migraine expecting the discovery of the definite explanation and treatment of the disease.

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