group studies which would destroy the local and internal nature of the audit they seek to evaluate.  
Audit should probably focus upon the process of care, but on the condition that the information generated is used to bring about appropriate change and that the change is then evaluated to show that it was effective. Perhaps this is the next step for audit in general practice.

Bibliography


For Debate . . .

Possible role of prostaglandin E₁ in the affective disorders and in alcoholism

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Summary and conclusions

Prostaglandin (PG)E₁ may play an important part in the affective disorders, with an excess being present in mania and a deficiency in depression. Platelets from manic patients produce more PGE₁ than normal while those from depressive patients produce less. Ethyl alcohol stimulates PGE₁ production whereas lithium inhibits it. Alcoholics will tend to have raised PGE₁ concentrations while drinking, but, because precursor supplies are limited, when alcohol concentrations fall PGE₁ concentrations may fall sharply leading to depression. PGE₁ biosynthesis may be affected by nutritional factors including essential fatty acids, pyridoxine, vitamin C, and zinc. Nutritional approaches may be of value in both depression and alcoholism.

Introduction

There is evidence to suggest that schizophrenia is associated with a deficiency of prostaglandin (PG)E₁ and with a raised dopamine:PGE₁ ratio. Recent work on the regulation of PGE₁ biosynthesis and action by lithium, alcohol, and tricyclic antidepressants suggests that this PG may also be important in the affective disorders and in alcoholism.

There are two main naturally occurring series of PGs, the PG₁ and the PG₂ series, named after the number of double bonds in their side chains. The PG₁ series are derived from dihomogamma-linolenic acid (DGLA) and the PG₂ series from arachidonic acid (AA). The PG₂ series have been thought to be overwhelmingly important because of the abundance of their
intracellular calcium. At higher concentrations this effect disappears. PGE1 in human platelets
AA, in almost all precursor, much of the actions while effects on Basic physiology (and then disturbances in regulation of substantial influence on human mental functioning.

Basic physiology

PGE1, the main product formed from DGLA, has substantial effects on excitable tissues. In isolated nerves very low concentrations increase conduction velocity and action potential amplitude, but as the concentrations increase the processes are first enhanced and then reversed. At low concentrations PGE1 opposes local anaesthetic actions while at high concentrations it imitates them.11 Similar results have been obtained in smooth muscle. At low concentrations PGE1 enhances the effects of agents that cause contractions by releasing intracellular calcium. At higher concentrations this effect disappears and then reverses. Many PGE1 effects may relate to modulation of release and reuptake of intracellular calcium, processes vital to both nerve conduction and the regulation of transmitter release. These processes probably occur at a basal level without PGE1. As PGE1 concentrations increase the processes are first enhanced and then inhibited. Since the PGE1 precursor is present in human brain,18 disturbances in regulation of PGE1 synthesis could possibly have a substantial influence on human mental functioning.

PGE1 in human platelets

In 1975 the British Journal of Psychiatry published a report which in retrospect may turn out to have been a landmark.14 It described the effects of adenosine diphosphate (ADP) on the formation of PGE1, by repeatedly frozen and thawed human platelets from normal individuals and from drug-free patients with diagnoses of mania, depression, or chronic paranoid schizophrenia. The methodology was complex, no one was interested in PGEs and mental illness, and the paper made no impact. Yet the findings were dramatic. Basal PGE1 concentrations in the four groups were not significantly different. At maximal ADP concentrations again there were no differences between normal, manic, and depressive patients but there was a severe deficit of PGE1 production in the schizophrenic patients (p < 10^-7). Using a much simpler technique, we have recently been able to show that this defect in schizophrenic patients can be imitated in normal platelets by high concentrations of opiate drugs.21

In relation to the affective disorders it is what happened at the half maximal ADP concentration that is of interest. At this point the normal, manic, and depressive patients were clearly separated with no overlapping between the values obtained in the three groups. Production of PGE1 in the platelets from the manic patients was significantly higher than that from the normal patients, which was in turn significantly higher than that from the depressive patients (fig 1).

Effects of drugs and other agents

PGE1 biosynthesis may be regulated at several points. Figure 2 shows some of them. The immediate precursor of PGE1 is DGLA. DGLA is an essential fatty acid that cannot be manufactured in the body. It or its immediate precursors, gamma-linolenic acid (GLA) or cis-linolenic acid (cLA), must be provided in the food. DGLA and GLA are present in food in only minute amounts, and the main dietary source is cLA, which is found in abundance in vegetable oils. Unfortunately the metabolism of cLA to GLA seems to be vulnerable to blockade by various factors. High fat and high carbohydrate diets, aging, excess of glucagon, and lack of zinc, pyridoxine, or insulin may all render the step inefficient.15-18 Hydrogenation of vegetable oils converts much of the cLA to the trans form. Thirty to forty per cent of the LA in margarine and foods prepared from hydrogenated and deodorised oils may be in the trans form. Trans LA cannot act as an essential fatty acid and may inhibit conversion of cLA to GLA.

Free DGLA is the immediate precursor of PGE1. Most DGLA is probably stored in the form of phospholipid esters. Control of PGE1 formation therefore depends on at least three factors—the provision of DGLA from dietary precursors, the conversion of esterified DGLA to free DGLA, and the conversion of free DGLA to PGE1.

The mobilisation of free DGLA has been studied in rat vascular tissue by indirect techniques.26-28 It seems to be inhibited by physiological concentrations of glucocorticoids and to be activated by physiological concentrations of prolactin, zinc, and melatonin. The reaction is inhibited by lithium ions.29-31 The threshold of the effect is at about 5-2 mmol/L, and it is maximal at 2 mmol/L. The therapeutic range of lithium concentrations in plasma is about 0-4 to 1-5 mmol/L, although recent reports of toxicity suggest that about 1 mmol/L is a sensible upper limit.

Until recently it had been assumed that any factor that modified conversion of free AA to 2 series PGs would affect conversion of DGLA in the same way. We have found this assumption to be untrue and that the reactions can be selectively regulated. In human platelets ethyl alcohol had no effects on conversion of AA to 2 series PGs but over a range relevant to human intoxication, 30-300 mg/100 ml (7-65 mmol/L), it greatly enhanced the formation of PGE1 from DGLA.32 Rotsos et al have recently made a similar observation, also in human platelets (submitted for publication). They also showed that ethanol in platelets could enhance the effect of PGE1 on cyclic adenosine monophosphate (AMP) formation. In rat brain slices the same concentrations of ethanol also potentiated the effect of PGE1 on cyclic AMP.

The mechanism of PGE1 action in excitable tissues is uncertain. It may have direct effects on membranes by itself but probably also works through two other mechanisms: the regulation of calcium movements and the formation of cyclic AMP.23 24 28 The calcium effect is biphasic, with enhanced release at low concentrations and reduced release at higher PGE1 concentrations. Two separate actions of PGE1 are probably concerned.23 Enhancement of calcium release may be a direct action of PGE1 whereas the inhibition of calcium release could be
mediated by cyclic AMP, which is known to have this effect. Tricyclic antidepressants may not have any effect on the biosynthesis of PGE, instead they seem able to inhibit intracellular calcium release, so opposing the effects of low concentrations of PGE, and imitating the effects of high concentrations.25 26

PGE, affective disorders, and alcoholism

The observations on platelets from patients with affective disorders, the basic physiology of PGE, and the effects of drugs on its biosynthesis and action suggest the following concept. PGE, is important not only in schizophrenia but also in the affective disorders and alcoholism. Its proposed actions on mental function are illustrated in fig 3. The peak effects of PGE, on excitable tissues seem to occur in the 10^{-11} to 10^{-16} mol/l range. Concentrations of PGE, in fluid bathing nerve cells are likely to be somewhat higher than this. PGE, concentrations in human blood and urine, away from the cells of origin and effect, or will exaggerate the PGE, deficiency in depression but will in the long term prevent depressive mood swings consequent on depletion of DGLA. Since such depressive changes will be blocked. The hypothesis predicts that with regard to calcium-dependent effects there will be another zone of normality (fig 3) in which PGE, concentrations are actually lower than in depressive patients. This could account for reports of treatment of depression with lithium. Possibly there may also be a group of genuine normal subjects in this zone: such people should become depressed rather than elated by alcohol.

(4) Tricyclic depressants at clinically relevant concentrations depresse calcium release and so would counteract the effects of PGE, concentrations in the “depressed” range.

(5) If one assumes that normal mood or a state of mild elation is desirable, then the concept predicts that depressive individuals will be particularly liable to become alcoholic once they discover the antidepressive, PGE, -raising actions of alcohol. Chronic overuse of alcohol will lead to depression when alcohol is not being consumed because of depletion of DGLA and its precursors. Such depression may be a reason for failure of rehabilitation.

(6) In individuals with depleted DGLA stores in whom even minimal levels of PGE, production are dependent on alcohol withdrawal of alcohol should lead to a drastic deficiency of PGE, and a syndrome with many of the features of schizophrenia. Measures to raise PGE, should alleviate this syndrome. Rotrosen et al have recently shown that PGE, could substantially alleviate the withdrawal syndrome in ethanol-addicted mice (submitted for publication).

(7) Inadequate formation of GLA as a result of inhibition of conversion of CLA to GLA should lead to psychiatric disturbances. Zinc deficiency, dietary pyridoxine deficiency, and glucagon excess may all lead to changes in behaviour, characterised by apathy and irritability.

(8) The concept proposes that there will be a continuum of mental states from schizophrenia through normality to depression and then from depression through another normal stage to mania. It suggests that there will be no sharp diagnostic cut-off points, although individuals who are unequivocally within the schizophrenic, depressive, or manic ranges may have clear-cut syndromes. It predicts that some features of mania and schizophrenia will be similar.

(9) Physical consequences of alcoholism may also be associated with depletion of essential fatty acids and reduced PGE, production. There are many similarities between the “feminised” state of the chronic male alcoholic and men with chronic zinc or essential fatty-acid deficiency. There are also similarities between the congenital abnormalities associated with zinc deficiency and with the fetal alcohol syndrome. Part of the effect may be due to alcohol depletion of zinc but part also to the fact that zinc deficiency and chronic alcoholism will lead by different routes to failure of normal PGE, production. There is also evidence that deficiency in zinc and in low PGE, concentrations, and possibly therefore alcoholic cirrhosis could be related to essential fatty-acid depletion.

Therapeutic implications

In depression the concept predicts that increasing PGE, synthesis or reducing the effect of PGE, on calcium-dependent processes should lead to improvement. PGE, biosynthesis is dependent on dietary provision of essential fatty acids and various co-factors. The diet should be rich in essential fatty acids in the cis form. There may be advantages in bypassing the potentially blocked stage by giving GLA or DGLA directly. Pyridoxine is necessary for the normal metabolism of CLA. Zinc is required for both formation of GLA and mobilisation of DGLA: there is evidence that marginal zinc deficiency is common. Tryptophan may enhance formation of both series of PGs while vitamin C selectively increases 1 series production, possibly accounting for the reported antidepressive effects of both these agents. Such a nutritional approach might well be more acceptable to many patients than drug treatment as a first line of attack.

In alcoholism the therapeutic aim would be to prevent DGLA depletion leading to a depressive state and to further craving for alcohol. This might be achieved by the oral or intravenous route. There have been reports of lithium use in alcoholism. It would not be expected to have any short-term effect but might prevent further excess mobilisation and therefore depletion of DGLA. Nutritional strategies should be of value in alleviating acute withdrawal symptoms, in reducing craving in the long term, and in preventing subsequent consequences of alcoholism such as cirrhosis.
effective and specific in controlling the acute syndrome, and we have heard verbal reports of their use for this in the 1930s and 1940s. If PGE$_1$ is excess is implicated then high doses of drugs that inhibit PG synthesis, such as indomethacin, might be of some value. Their effect would not be specific since they inhibit 2 series PG formation as well, and high doses would be required since brain PG synthesis seems relatively resistant to their effects.

Conclusions

Quite obviously this is an oversimplified scheme that represents nothing more than a first attempt at relating PG, series to the affective disorders and alcoholism. We have no desire to downgrade the importance of catecholamines, indoles, amino-acids, peptides, or PG$_2$ series. These other agents are almost certainly implicated in the affective disorders, and variations in their rates of synthesis and in their actions are likely to make major contributions to the almost infinite variety of clinical syndromes. On the other hand, the PGE$_1$ concept does seem relatively successful in explaining several well-established observations. It also suggests completely new approaches to the treatment of depression by nutrition and to the search for new types of antidepressant drugs. Since the PGE$_1$ effects on calcium-dependent processes and on cyclic AMP are likely to modify release of and responses to all other neurotransmitters, the PGE$_1$ concept should not be ignored by proponents of other views of affective disorders.

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References


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A married woman in her 30s has persistent attacks of cramp in both calves when in bed. They started after her second child seven years ago. Investigation shows no abnormality. What might be the cause, and what treatment is advised?

Cramp is essentially muscular spasm. Muscle in the legs is mainly skeletal, but arterial and venous muscle must also be considered. Cramps are usually excluded by investigation, especially the possibility that the cramps arise in varicose veins. Some cramps might be caused by nerve entrapments, so that the lower back and pelvis need investigation. Known causes of muscular spasm include salt and calcium deficiencies. These may or may not be important, and such localised cramps, but a trial of a glass of milk at bedtime or a salty drink would do no harm and might help. Cramp in pregnancy, which is common, often yields to calcium given as tablets or in milk. Finally, this might possibly be a sign of malabsorption, requiring much deeper investigation.