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PHARMACOLOGICAL EFFECTS OF SOME MEDICAMENTS ON THE HUMAN BRAIN

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Summary

The methodological problems of measuring the effect of drugs on cerebral blood flow (CBF) are examined. In animals these include choice of species, technique of measurement, route of administration and whether the drug crosses the blood-brain barrier. Additional factors in man are age, short or long-term effects, tendency for repeated measurements to give lower readings and need to measure not only CBF but also clinical performance. Despite these difficulties drugs affecting the cerebral circulation are worth intensive study, especially now, when reliable non-invasive methods of measuring CBF are available and positron emission tomography enables us to study also cerebral metabolism in vivo.

Zusammenfassung

Die methodischen Probleme zur Beurteilung der Wirkung von Medikamenten auf die Hirndurchblutung werden dargelegt. Bei Tierversuchen spielt die Wahl der Tiergattung bzw. -art, die Messmethode, der Applikationsmodus des Medikamentes und dessen Blut-Hirnschrankengängigkeit eine Rolle. Beim Menschen müssen Alter, Kurz- und Langzeitwirkung (und Nebenwirkungen), Wiederholbarkeit der Messungen und die Notwendigkeit der Bestimmung von Hirndurchblutung und klinischen Parametern zusätzlich berücksichtigt werden. Die Untersuchungen über die Wirksamkeit von cerebrovaskulär aktiven Substanzen sind trotz diesen Schwierigkeiten vertretbar und nützlich, sofern nichtinvasive zuverlässige Verfahren zur Messung der regionalen Hirndurchblutung und des lokalen Energiestoffwechsels zur Verfügung stehen, wie dies mit der intravenösen Xenon-Clearance Technik und der Positron-Emissions-Tomographie möglich ist.

The list of drugs which affect cerebral function is as long as the pharmacopoeia itself for almost every drug in one way or another, directly or indirectly, affects the brain. The present paper is concerned with that group of drugs commonly referred to as cerebral vasodilators. Restricting the scope of the paper in this way still leaves us with problems. Cerebral blood flow (CBF) is closely linked to cerebral metabolism, hence it can be argued that low flow simply reflects reduced metabolic needs. On this hypothesis measuring flow carries little purpose if the brain, by reason of the disease affecting it, cannot make use of the increased supply of oxygen, glucose and other substances. Drugs which will stimulate cerebral metabolism and overcome the metabolic defect are required; blood flow will then increase accordingly, except in those cases in which occlusions of arteries or structural changes in the vessel walls prevent this. However the problem is not so simple as this hypothesis would suggest.

Before turning to the drugs themselves there are some important methodological points about the testing of their effects on CBF in both animals and man which must be appreciated. Without some background knowledge it is impossible to assess the many reports on drug effects which abound in the literature or to understand the discrepancies which they contain.

The most important factor in the choice of animal is whether or not it has a rete mirabile; the cat family, cloven-hoofed animals and the rhinoceros possess a rete; the rat, rabbit, dog, horse and man do not. The rete is not merely a large passive reservoir; there is evidence, certainly from the goat, that the vessels of the rete autoregulate. The effect this may have upon the cerebral circulation is clearly immense. Even in species without a rete such as the dog it is important to be aware that the major blood supply to the brain is via the external, not the internal, carotid artery.

The second factor to be considered is the technique of measuring CBF. Flow meters over major feeding vessels have their place, but clearly if it is total brain perfusion we are interested in, the anatomical factors mentioned above must be taken into account. It is no use measuring flow in the internal carotid artery if the major blood supply to the brain is via the external carotid artery. Transit times of markers through the cerebral circulation have been extensively used but here again care is required in interpreting results. More rapid transit does not mean better perfusion; it may simply reflect a decrease in the vascular bed so that to maintain the same perfusion blood must flow more quickly.

The best measure is undoubtedly that of cerebral perfusion which can readily be made by isotope clearance techniques. All that is required is a freely diffusable metabolically inert substance such as ^{133}Xenon. The arrival and rate of removal of the isotope from the brain, which can be monitored by external detectors, provides clearance curves which can be computed so as to give a measure of cerebral perfusion.

Turning now to the drugs themselves, a most important factor is the mode of administration. The existence of the blood-brain barrier means that drugs, even if given into the internal carotid artery, may have no effect upon CBF, whereas if they are applied externally to the cerebral vessels they are dramatically effective. The blood brain barrier can be breached by intracarotid administration of a hypertonic solution such as urea.

This may not be a very physiological procedure but if, as a result, a subsequently administered drug is shown to increase CBF it becomes worth while pursuing further studies to discover if a precursor can be made to reach the brain. There is a striking parallel in the treatment of Parkinsonism; dopamine was ineffective because it did not cross the barrier; its precursors L-dopa crossed the barrier and so a major therapeutic advance became possible.

Finally, in considering drugs the question of dose must not be forgotten. Failure to produce an effect may simply mean too small a dose has been used. A large increase may be equally ineffective because though the response is proportional to the drug up to a point, beyond that point a reverse response is obtained. A dose response curve is required.

These various points may seem so obvious as not to require mention but it is surprising how often they are neglected in reports on drugs and CBF in animal experiments.

Turning now to man, assessment of the effect of drugs on CBF involves three stages. Firstly, it is necessary to show that acute injection of the drug increases CBF; secondly, it must be shown that short and long-term oral ingestion raises and maintains a higher level of CBF; thirdly, the long term increase in CBF must be shown to benefit the patient in terms of psychological performance or activities of daily living.

Here again there are technical points to be remembered. Any measure of CBF which is not accompanied by measurement of pCO_2 is valueless as slight change in pCO_2 (which is the most potent vasodilator we have) will profoundly alter CBF. Yet one still finds papers published in which no data on pCO_2 are provided.

The age of the subjects must also be taken into account. Using the intravenous ^{133}Xenon clearance technique we found the CBF to be 77.1 ml/100 g/min in a group of normal subjects under the age of 45 years falling progressively in each decade to 60.4 ml/100 g/min in those over 65 years (1). Finally, allowance must be made for the effect of repeated estimations upon CBF. In anaesthetized patients a second CBF measurement shortly after a first measurement by the intracarotid ^{133}Xenon technique showed a fall in CBF of 24 per cent. In awake patients the fall was less but still was of the order of 10 per cent (2). This can be counteracted by keeping the patient alert. In the longer term - over a period of three weeks - a decline in CBF of the order of 9 per cent is almost invariable (1) and could well obscure the degree to which a drug had raised the basic level of CBF.

There are yet other problems which must be faced, prominent among which is the fact that the cerebrovascular tree cannot be considered as a whole. The major feeding vessels are innervated by sympathetic fibres from the superior cervical ganglion. The pial vessels have both adrenergic and cholinergic innervation. The parenchymal vessels have adrenergic fibres but these derive from the locus coeruleus and not from the extrinsic sympathetic system. Recently actin and myosin have been identified in capillary walls hence capillaries may not merely reflect passively the effects of arterial and venous pressure but may be capable of an intrinsic response.

An example of the differential response of parts of the vascular tree is provided by hypotension which constricts proximal vessels as part of the generalized systemic vasoconstriction but dilates peripheral cerebral vessels. Another example is that of CO_2 which normally dilates proximal and distal vessels, but if the animal is hypotensive CO_2 dilates proximal vessels only; distal vessels constrict.

Against this complex background it is hardly surprising that reports on the effects of cerebral vasodilators in man are confusing and often contradictory. The following summary is based on trying to determine a consensus among the studies which best fulfil the criteria outlined above.

Papaverine, hexobendine, acetazolamide, histamine, cyclandelate, meclofenoxate, pentifylline nicergoline and tinofedrine increase CBF. In some the increase is transient and in others such as papaverine the drug is clearly not suitable for regular clinical use.

Uncertainty exists about isoxsuprine, naftidrofuryl, amphetamine, 5-hydroxytryptamine, dopamine and nylidrin, as both increase and decrease of CBF have been reported.

Vincamine when given into the internal carotid artery has been reported to restore reduced CBF to normal in acute strokes; it had no effect if the CBF was already normal.

Some of the agents used in the treatment of hypertension have been studied, both methyl dopa and propanolol increasing CBF.

Dihydroergotoxine mesylate and naftidrofuryl do not increase CBF but there is evidence that they stimulate cerebral metabolism which emphasizes the point that it may be better to increase metabolism, which will in turn increase CBF, rather than making an increase of CBF the primary therapeutic target. The development of positron emission tomographic scanning seems likely to provide a powerful new tool for the study of cerebral metabolism in man in vivo. As both CBF and metabolism can be measured by this technique the next decade is likely to see exciting new developments in this field.

Clearly, in the light of these results it is difficult to draw any firm conclusions about the role of cerebral vasodilators in general, let alone about any drug in particular. This brings us back to the point that in general the CBF is appropriate to the metabolic needs of the brain. In patients with multi-infarct dementia in whom we showed CBF to be low, giving CO_2 increased flow indicating that it was not inability to supply the blood but lack of demand for it that was at fault (3). What then is ischaemia due to? Pathological evidence indicates it is the result of multiple small infarcts caused either by emboli or by localized disease in the wall of small vassels.

Paradoxically this conclusion does not exclude a role for cerebral vasodilators. In the case of emboli and possibly in other instances, flow has an influence on whether the embolus adheres, propagates and produces infarction or whether it disintegrates and moves on leaving the parenchyma intact.

There are drugs which increase cerebral perfusion in the short-term at least. What is now required is well designed and well executed studies - which pay proper regard to the points set down in this paper - of short and long-term effects of these drugs on CBF and on cerebral metabolism. This is a promising field of endeavour calling for collaboration between physicists, pharmacologists, experimentalists, clinicians and others. Given this collaboration the next decade should give us interesting and worth while results.

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