

CEREBRAL BLOOD FLOW AND METABOLISM IN ANXIETY AND ANXIETY DISORDERS

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Anxiety disorders are some of the commonest psychiatric disorders and anxiety commonly co-exists with other psychiatric conditions. Anxiety can also be a normal emotion. Thus, study of the neurobiological effects of anxiety is of considerable significance. In the normal brain, cerebral blood flow (CBF) and metabolism (CMR) serve as indices of brain function. CBF/CMR research is expected to provide new insight into alterations in brain function in anxiety disorders and other psychiatric disorders. Possible associations between stress / anxiety / panic and cerebral ischemia / stroke give additional significance to the effects of anxiety on CBF. With the advent of non-invasive techniques, study of CBF/CMR in anxiety disorders became easier. A large numbers of research reports are available on the effects of stress, anxiety and panic on CBF/CMR in normals and anxiety disorder patients. This article reviews the available human research on this topic.

Key words: cerebral blood flow, cerebral metabolism, anxiety, anxiety disorders, obsessive compulsive disorder, panic disorder, generalized anxiety disorder, sympathetic stimulation.

INTRODUCTION

The word anxiety means being troubled in mind about some uncertain event, being in disturbing suspense, being fraught with worry, etc. The ineffable feeling of foreboding is regarded as the central core. When the cause for the emotion is clear, the word fear is preferred. Anxiety as part of everyday experience, can be a normal emotion. But it can also be an abnormal one and distinctions between normal and abnormal are difficult. Operationally, abnormal anxiety has been identified as causing the sufferer to seek relief. Another distinction is based upon the relationship of the intensity / duration of the emotion to the apparent cause, abnormal anxiety being disproportionately excessive. No qualitative differences have been demonstrated between normal and abnormal anxiety (Lader, 1982). Intensity of anxiety associated with a given situation is a function of the anxiety proneness of the individual and the degree of threat perceived by him/her. Anxiety disorders are some of the commonest psychiatric illnesses and they commonly co-exist with other physical and mental disorders. A number of disorders which differ in clinical characteristics have been subsumed under anxiety disorders (DSM-III-R)

RELEVANCE

The relationship between anxiety and cerebral blood flow (CBF) is of considerable significance for a variety of reasons. As was pointed out earlier, anxiety disorders are some of the commonest psychiatric disorders and anxiety is present in almost all other psychiatric disorders (Kessler et al, 1985;

Regier et al, 1988). Anxiety as a normal emotion is a part of day to day existence. Thus, understanding of the physiology of anxiety will be relevant to the entire field of psychiatry.

Cerebral anoxia is the most important clinical manifestation of reduced CBF. Such symptoms as dizziness, unsteadiness, light headedness and fainting (DSM III-R) are often seen in anxiety disorder patients and may be indicative of cerebral anoxia. Blood pressure reduction via vasovagal mechanisms and consequent cerebral ischemia are commonly held responsible. However, alternate explanations are available and no firm conclusions are justified.

In a study of nineteen patients with panic disorder and twenty six with generalized anxiety disorder, patients had a significantly higher prevalence of symptoms suggestive of cerebral ischemia as compared to controls; 47% reported dizziness, 32% loss of speech, 37% tingling and 16% weakness and paralysis (Mathew et al, 1987). Among three hundred and fifty referrals to a neurology service, 5% had panic attacks manifesting as focal neurological symptoms lasting approximately fifteen to thirty minutes. All patients experienced, simultaneously two or three different neurological symptoms, including sensory, motor, visual and vestibular symptoms and headache. The most frequent sensory symptom was numbness and tingling in a hemi-sensory distribution or localized to one extremity. Motor symptoms included clumsiness or a feeling of heaviness of an extremity. Bilateral blurring or total blindness, often associated with visual distortions were seen. Hyperventilation which reduces CBF (Fried, 1987; Mathew & Wilson, 1988; Maximilian

et al, 1980) reproduced the specific symptoms in 42% of the patients (Coyle & Sterman, 1986). Focal neurological symptoms indicate reduced regional (as opposed to global) CBF and argue against reduction in blood pressure vasovagal mechanisms (which is more likely to produce global CBF decrease). Reduction in global CBF usually results in dizziness and fainting but cannot explain focal neurologic symptoms in individuals with no pre-existing abnormalities of cerebral circulation. It should be noted that the patients studied by Mathew et al (1987) and Coyle and Sterman (1986) did not suffer from any neurological or circulatory disease.

Anxiety disorder patients often complain of headaches. In all probability, tension headaches and anxiety are closely related; the relationships between vascular headaches and anxiety are less clear (Headache Classification Committee of the International Headache Society, 1988). A number of research reports are available on intra and extra-cranial blood flow changes associated with various types of headaches (Olesen, 1991). Sympathetic activation may play a causal role in at least certain types of headaches (Mathew et al, 1982a). Information regarding CBF changes associated with anxiety will give new insights into the vascular mechanisms related to headaches.

Several case reports and epidemiologic studies identified stress and anxiety as risk factors for stroke (Adler et al, 1971; Leonberg & Elliott, 1978; Weissman et al, 1990). However, there usually listed among the established risk factors for stroke (Haberman et al, 1982) although their relationship to coronary artery disease is well accepted (Mathews et al, 1986). Coronary heart disease is a risk factor for stroke (Wolf et al, 1978). More research, both population studies and laboratory studies, need to be conducted on stress/anxiety and stroke.

Stimulants and most hallucinogens induce sympathetic activation (as in anxiety) manifested by increased pulse rate, blood pressure, respiration and perspiration. Most subjects do not experience this sympathetic activation as unpleasant; as a matter of fact, drug-induced sympathetic stimulation usually co-exists with euphoria (Mathew & Wilson, 1985a; Lake, 1988; Gawin & Ellinwood, 1988). However, less frequently, these drugs can produce anxiety and panic and such symptoms as restlessness, agitation, irritability, distractibility, etc (Charney et al, 1985; Gawin & Ellinwood, 1988; Anthony et al, 1989). Withdrawal from yet other drugs of abuse such as ethyl alcohol, benzodiazepines and barbiturates are

associated with central and peripheral symptoms of sympathetic activation and anxiety (Hawley et al, 1985; Mellman & Uhde, 1986; Foy et al, 1988; Thomas et al 1989, George et al, 1988). According to some investigators, stimulant intoxication and sedative (alcohol) withdrawal decrease CBF (Berglund et al, 1981, Mathew and Wilson, 1991). Drugs of abuse, especially stimulants and alcohol have also been implicated in the causation of cerebral ischemia and stroke (Caplan et al, 1982; Levine & Welch, 1987; Sloan et al, 1991, Mathew & Wilson, 1991). Cerebral blood vessels are innervated by vasoconstrictive sympathetic fibers (Edvinsson et al, 1993). Thus, the relationship between anxiety and CBF will be of importance to CBF changes during drug (sympathetic agonists) intoxication and (sedatives, hypnotics) withdrawal (Mathew & Wilson, 1991).

MEASUREMENT TECHNIQUES

Study of global and regional alterations in CBF became easier with the advent of less invasive measurement techniques (Mathew et al, 1985). In the normal brain, CBF and Cerebral metabolism (CMR) serve as indices of brain function (Figure 1). Functional psychiatric disorders are believed to be caused by abnormal brain function, which is the main reason why CBF and CMR are used in psychiatric research. Techniques such as the ^{133}Xe intra-carotid injection and inhalation techniques, Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET) measure CBF; PET can also be utilized for the quantification of CMR for glucose and oxygen (Mathew et al, 1985; Mazziotta, 1985).

These techniques vary in the degree of invasiveness with the intra-carotid ^{133}Xe injection technique being the most invasive and therefore, the least utilized, at present. Invasiveness of the technique is very important especially in anxiety research, for obvious reasons. Quantification of absolute CBF with PET require arterial punctures (Mazziotta, 1985). Arterial punctures induce varying degrees of anxiety in patients as well as normals and the sensation of pain, on its own right, might increase CBF (Ingvar & Lassen, 1976). Less invasive PET techniques for CBF/CMR measurements are being developed. It is difficult to calculate absolute CBF with SPECT except when ^{133}Xe is used as the tracer in which case spatial resolution is less impressive. All of the above mentioned techniques have the disadvantage of the known and unknown risks as-

sociated with radiation exposure. More recently, Magnetic Resonance Spectroscopic (MRS) techniques which do not involve any radiation exposure have been developed for the measurement of CBF and CMR (Lock et al, 1990). Unfortunately, most of these MRS techniques do not provide absolute quantitation. MRS techniques have not been widely used in psychiatric research.

Trans-Cranial Doppler (TCD) Sonography can be used to measure cerebral blood velocity (CBV) through major intracranial arteries (Aaslid et al, 1982; Aaslid & Lindergaard, 1986). CBV is determined by the perfusion pressure (arterial blood pressure minus venous pressure) and resistance to flow (intracranial pressure and cerebral vascular resistance) in the brain. Thus, if the perfusion pressure

and intracranial pressure are within normal limits with minimal fluctuations, CBV can serve as an index of CBF. However, TCD does not give information about regional CBF. Its major advantages are absence of radiation exposure, total non-invasiveness, simplicity, ability to measure CBV in different positions (lying, sitting and standing) and ability to measure CBV every thirty seconds. The last feature will provide useful information about the dynamic changes in CBF especially after anxiety induction. TCD has been used to study the effects of psychotropic drugs on cerebral circulation (Mathew et al, 1992 a, b & c).

PHYSIOLOGY

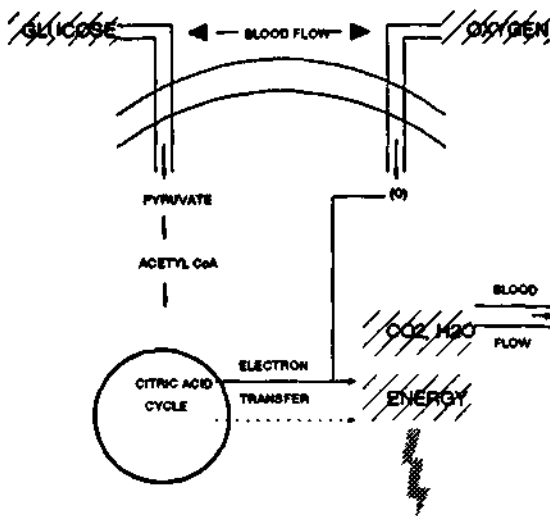
A great deal of information is currently available on CBF physiology (Busija & Heistad, 1984 a; Mathew et al, 1986; Edvinsson et al, 1993). Anxiety is associated with many physiological changes a number of which may be relevant to CBF (Figure 2). Both central and peripheral factors related to anxiety can influence CBF. It is important to note that anxiety related CBF changes are most likely to be influenced by a variety of factors other than brain function. Although an impressive volume of basic science research has confirmed their relevance (Edvinsson et al, 1993), unfortunately, factors other than brain function have not received the importance they deserve in contemporary, CBF/CMR research in psychiatry. Such factors are especially important in anxiety/CBF research.

AROUSAL

Nonspecific arousal is believed to be the neurobiologic substrate for anxiety (Lader, 1982; Moruzzi & Magoun, 1949; Malmö, 1959). The brain stem reticular activating system generates generalized, diffuse activation of the brain. Anxiety is associated with high levels of arousal while low arousal is associated with drowsiness, sleep and coma. Since CBF is closely coupled to brain function, CBF increase will be expected in high arousal states and decrease, in low arousal states. Indeed, CBF reductions have been reported in semicoma, stupor and slow wave sleep; activation and epileptic seizures being associated with increased CBF (Townsend, 1973; Ingvar and Lassen, 1976; Mathew, 1989; Mathew & Wilson, 1990; Mathew et al, 1993 c).

The brain stem reticular activating system terminates in the reticular nuclei of the thalamus from where cortical and other limbic connections originate (Nauta, 1971; Stuss & Benson, 1986; Feir-

Figure 1
Energy Metabolism



Cerebral blood flow and metabolic rates for glucose or oxygen may be used as indices of brain energy metabolism

In the normal brain, blood flow and metabolism are closely coupled with brain function. Cerebral blood flow delivers glucose and oxygen to the brain and removes the metabolites, carbon dioxide and water. Glucose and oxygen are directly related to the energy metabolism.

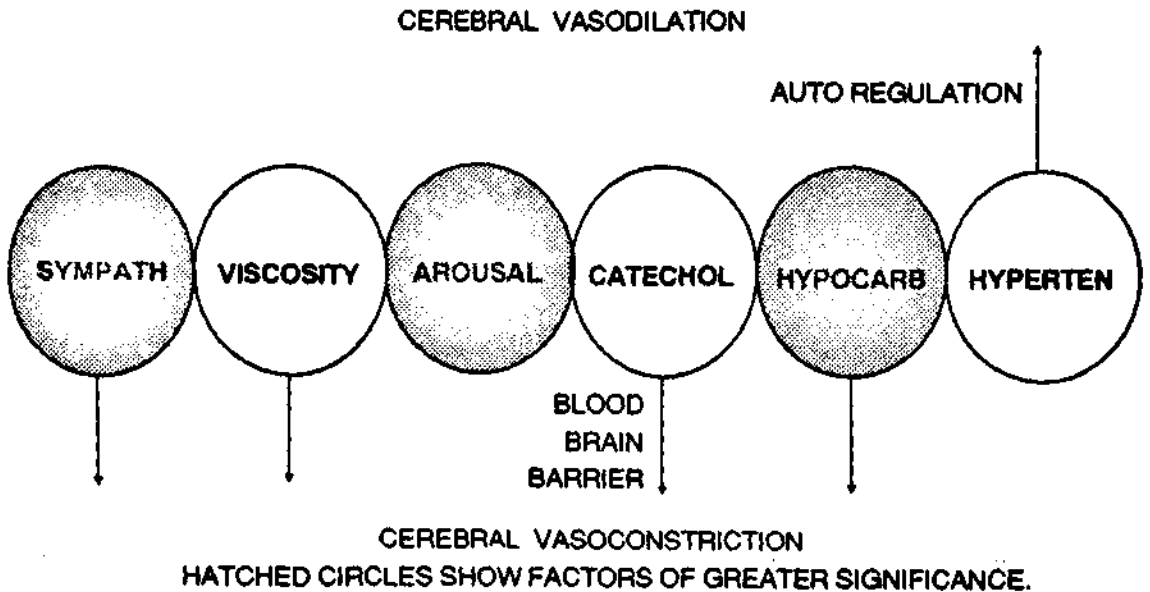
tag & Nauta, 1986). Thalamo-frontal connections are well known since these fibers are commonly interrupted in psycho-surgical techniques (Kelly, 1986). The frontal lobe has been identified as the "cortical representative" of the arousal system. The well known EEG pattern of predominately high frequency / low voltage wave-forms over the frontal lobe during wakefulness lends support to the concept of frontal activation during arousal (Ingvar, 1979; Ingvar & Soderberg, 1958; Menon et al, 1980).

Most of the studies conducted with the intra-carotid ¹³³Xenon injection and ¹³³Xenon inhalation studies found higher frontal flow during resting wakefulness (Ingvar, 1979; Mathew et al, 1986; Weinberger et al, 1986; Mathew et al, 1988). However, more recent studies with the three dimensional CBF techniques (PET, SPECT) failed to replicate this finding (Lauritzen et al, 1981; Rapoport et al, 1985; Devous et al, 1986). It is unclear whether this discrepancy is due to physiologic or technologic reasons (Mathew, 1989).

Behavioral and pharmacological activation of the brain seems to augment frontal circulation. Techniques used to increase activation include problem-solving test, word-pair learning and recall, digit-span backward test and reasoning test, right-left discrimination test, the Wisconsin Card Sort, sensory stimulation and a variety of attention-demanding tasks (Risberg et al, 1977; Maximilian et al, 1978; Risberg & Ingvar, 1973; Leli et al, 1983; Risberg & Prohovnik, 1983; Weinberger et al, 1986; Deutsch et al, 1987a). It needs to be pointed out that some investigators could not find increased frontal flow during the administration of the Raven's progressive matrices and right-left discrimination test (Berman et al, 1988, Leli et al, 1982). Euphoria associated with marijuana increased global CBF with most marked changes in the frontal lobes. The CBF increase seen after marijuana smoking was unrelated to plasma THC and possibly, peripheral vasodilation (Mathew & Wilson, 1993).

Studies have also been conducted on CBF during reduced arousal. Slow wave sleep attenuates frontal

Figure 2
Anxiety related factors relevant to CBF and the directions of their effects



Sympath: sympathetic activation, Viscosity: blood viscosity, Arousal: non-specific arousal mediated by the reticular activating system, Catechol: catecholamines, Hypocarb: hypocarbia (hypocapnia), Hyperten: hypertension.

Anxiety is associated with a number of factors which can influence CBF in either direction. Known factors, the directions of their effects and their relative importance are shown.

flow and hyperfrontality is absent in comatose states (Townsend et al, 1973; Deutsch & Eisenberg, 1987b; Madsen & Vorstrup, 1991). Tranquilization induced with non-sedating doses of diazepam reduced frontal perfusion (Mathew et al, 1985). Similarly, haloperidol decreased global including neocortical CMR glucose, after twelve hours (Bartlett et al, 1994).

It seems safe to conclude that global CBF has a parallel relationship with arousal states. Most available studies but not all, suggest that arousal related CBF changes are most marked in the frontal lobe.

HYPOCAPNIA

Carbon dioxide is very well known as a potent cerebral vasodilator (Maximilian et al, 1980; Mathew & Wilson, 1988). Hyperventilation characterized by increased rate and depth of respiration and hypocapnia, is a common symptom of acute anxiety and panic (Fried, 1987). Hypocapnia in turn, can induce cerebral vasoconstriction. Indeed, CBF reduction due to reduced CO₂ has been implicated in several anxiety related symptoms (Fried, 1987). As was pointed out earlier, hyperventilation can produce focal neurological symptoms suggestive of cerebral ischemia in panic disorder patients (Coyle and Sierman, 1986). Panic disorder patients may show an exaggerated CBF decrease during hyperventilation (see below: Gibbs, 1992).

AUTONOMIC NERVOUS SYSTEM

A great deal of literature is available on the relationship between anxiety and autonomic nervous system activation (Lader, 1975). Such effects of acute anxiety on blood circulation as increased heart rate, increased blood pressure, reduced skin circulation and increased muscle flow are due to stimulation of the sympathetic division of the autonomic nervous system. Thus, sympathetic innervation of cerebral blood vessels can be of considerable significance.

Sympathetic nerve fibers reach cerebral blood vessels through three routes. Post-ganglionic fibers from the superior cervical ganglion innervate vessels in the carotid territory. The vertebro-basilar territory is innervated by the stellate ganglion. Lastly, fibers from the stellate ganglion may follow the tunica adventitia of the common and internal carotid arteries to reach the circle of Willis. There is progressive reduction in the number of sympathetic fibers as the vessels become smaller; larger arteries which travel up through the brain tissue from brain-stem nuclei such as locus ceruleus can be found on or near

cerebral microvessels (Edvinsson, 1982; Edvinsson et al, 1993). Cerebral blood vessels contain both alpha and beta adrenergic receptors (Nathanson, 1983). The sympathetic fibers also influence CMR, blood brain barrier permeability and CBF production (Edvinsson et al, 1993).

LESS RELEVANT FACTORS

Other anxiety related physiological changes such as an increase in the blood levels of epinephrine and norepinephrine and changes in blood viscosity are unlikely to be very relevant. Peripheral epinephrine and norepinephrine are destroyed by the blood brain barrier which contain such enzymes as monoamine oxidase (MAO) and catechol O methyl transferase (COMT) (Edvinsson & MacKenzie, 1976; MacKenzie & Scatton, 1987; Edvinsson et al, 1993). Anxiety related increase in blood viscosity (otherwise known as stress polycytosis) seems to be too modest to influence CBF (Dameshek, 1953; Mathew & Wilson, 1986 & 1987). Anxiety related increases in pulse rate and blood pressure are unlikely to be of relevance since CBF is insulated from modest changes in blood pressure (autoregulation) (Strandgaard & Paulson, 1984; Paulson et al, 1990).

CBF DURING UNPROVOKED ANXIETY

Even non-invasive measurement of CBF can be stressful especially to lay individuals unaccustomed to hospitals and laboratories. Most measurement techniques involve sophisticated machinery which can induce apprehension. Anxiety associated with exposure to the measurement technique can vary from none to very severe. A number of investigators looked at the relationship between anxiety associated with the measurement technique and CBF/CMR. Mild to moderate degrees of anxiety caused CBF increase but more severe anxiety had the opposite effect. High anxiety also had a negative relationship with cerebral metabolism (Gur et al, 1987; Rodriguez et al, 1989).

The first CBF measurement will be expected to produce more anxiety than the second and their measurements. In normal volunteers, when CBF was measured repeatedly during rest, values decreased from the first to the second measurement. This CBF decrease was most marked in the frontal regions (Warach et al, 1992). Gur and colleagues (1987) found a positive relationship between CBF and anxiety when the anxiety was mild. However,

with more severe anxiety, CBF declined. Rodriguez and associates found an inverse correlation between CBF and state anxiety in sixty neurologically normal patients. These inverse correlations were most significant in the right frontal region.

Other investigators examined the relationship between anxiety during the measurement of CMR with PET. Reivich and associates (1983) found a curvilinear relationship between fronto-cortical metabolism and anxiety. However, anxiety during measurement of CMR glucose was found to have no effect by Giordani and colleagues (1990). Other investigators also found minimal or no relationships between CMR and anxiety associated with the procedure (Duara et al, 1984; Buchsbaum et al, 1985).

Anxiety disorder patients who are more anxiety prone are likely to experience more anxiety during the procedure than normal volunteers. Studies on the relationships between anxiety and resting CBF/CMR have been conducted in patients with generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD) and panic disorder. In patients with generalized anxiety disorder, state anxiety and CBF showed an inverse correlation (Mathew et al, 1982). Anxiety in OCD patients also significantly correlated inversely with CBF (Machlin et al, 1991). In another study of OCD patients, state anxiety during CMR measurement with PET correlated significantly with right prefrontal, left prefrontal and right orbital CMR (expressed as ratios to the mean cortical CMR). OCD patients who panicked showed significantly lower left premotor and higher right prefrontal CMR (Swedo et al, 1987).

It is well known that many but not all, panic disorder patients experience panic attacks during lactate infusions. In lactate sensitive panic disorder patients, under resting conditions, a significantly lower right to left ratio in the parahippocampal gyrus blood flow in comparison to the lactate insensitive panic disorder patients and normals was found (Reiman, 1984). Lactate sensitive patients also had abnormal asymmetries of parahippocampal blood volume and metabolic rate for oxygen. Analysis of parahippocampal measurements on each side separately suggested an abnormal CBF increase in the right side in lactate sensitive panic disorder patients. They also showed a significantly higher whole brain metabolic rate for oxygen (Reiman et al, 1986).

Nordhal and associates (1990) conducted a similar study. Panic disorder patients, during auditory discrimination tests were found to show asymmetry of CMR glucose in the hippocampus; however, they did not show any abnormalities of global grey matter metabolism.

In summary, it seems fairly clear the mild anxiety is associated with CBF increase. Higher CBF during the first as compared to the second CBF measurement is well established and it provides firm support for this notion. It is possible that more severe anxiety decreases CBF. Under resting conditions, frontal CBF is higher than the rest of the brain and during repeated measurement, frontal CBF shows most marked reduction. There are only few studies on regional CBF/CMR in panic disorder patients, under resting conditions. Available literature suggests asymmetry of CBF/CMR in the hippocampal/parahippocampal region.

There are only few studies on CMR and resting levels of anxiety. Of the available studies in panic disorder and OCD, results vary widely. Thus, effect of resting anxiety on CMR is less certain.

ACTIVATION STUDIES IN NORMALS

Several investigators utilized specific strategies to induce stress in normal volunteers. Techniques used included mental arithmetic tasks (Sokoloff et al, 1955) and speaking and counting (Shakhnovich et al, 1980). It should be noted that brain function and CBF are coupled and therefore, perception of the sensory stimulation associated with the stress inducing task on its on right, should increase CBF in the corresponding brain regions. In earlier studies which measured global flow with no separation between grey and white matter flow, no CBF changes were seen during sensory stimulation associated with stressful tasks. More modern techniques which separated brain regions and grey from white matter showed CBF increase in sensory regions and increase in global flow during activation studies (Risberg et al, 1977; Maximilian et al, 1978; Risberg and Ingvar, 1973; Leli et al 1983; Weinberger et al, 1986; Risberg & Prohovnik, 1983; Deutsch et al, 1987). Most investigators did not report degrees of anxiety during the procedures.

CBF DURING PHARMACOLOGICALLY PROVOKED ANXIETY

A wide variety of pharmacological techniques were utilized to examine the relationship between

induced anxiety and CBF. Caffeine is well known to induce anxiety in normal subjects, anxiety disorder patients and especially, those with panic attacks (Charney et al, 1985; Gorman, 1987). Caffeine is a powerful cerebral vasoconstrictor (Mathew & Wilson, 1985b). However, intravenous administration of 250 milligrams of caffeine did not induce anxiety in GAD patients and there were no significant difference between GAD patients and normals on caffeine induced cerebral vasoconstriction. (Mathew & Wilson, 1990). Epinephrine infusions on the other hand, produced significant increases in state anxiety, respiration and pulse rate. However, there were no significant differences between GAD patients who received epinephrine and saline on hemispheric or regional CBF, though, in the epinephrine group, significant inverse correlations were found between state anxiety and left and right hemispheric CBF (Mathew et al, 1982b, Mathew & Wilson, 1989a).

Carbon dioxide inhalation is another technique used by several investigators for anxiety induction, especially in panic disorder patients (Gorman, 1987). As was mentioned earlier, CO₂ is a powerful cerebral vasodilator (Maximilian et al, 1980). In our hands, CO₂ inhalation did not induce more state anxiety in GAD patients as compared to controls. Both patients and controls showed similar cerebral vasodilation during 5% CO₂ inhalation. However, some of the patients and controls reported increased anxiety during the procedure and those who showed anxiety increase also showed less marked increases in CBF. There was a significant inverse correlation between CBF and state anxiety for the entire group during CO₂ inhalation. Thus, the results indicated that subjects who became anxious during 5% CO₂ inhalation showed less marked CBF increase (Mathew & Wilson 1988 & 1989b). This finding supported the notion of cerebral vasoconstriction during severe anxiety.

Acetazolamide is known to inhibit carbonic anhydrase which normally catalyzes the hydration of CO₂ and hydrolysis of carbonic acid. Thus, acetazolamide injections result in hypercapnia. Panic disorder patients who received intravenous injections of acetazolamide did not develop panic attacks. However, both panic disorder patients and normals after the drug, showed significant CBF increases. Once again some of the subjects from the panic disorder group and normal controls reported increased anxiety after the injection and those who became anxious showed less marked cerebral vasodilation (Mathew et al, 1989).

Although carbon dioxide inhalation is reported to precipitate anxiety, hyperventilation and hypocapnia have also been found to cause panic attacks (Gorman et al, 1988; Maddock & Carter, 1991). It is possible that the distress caused by both hyper and hypocapnia precipitates panic in predisposed patients.

Gibbs (1992) examined cerebral blood velocity (CBV) of the basilar artery with TCD in nine panic disorder patients and nine controls, both under resting conditions as well as during hyperventilation. Panic disorder patients showed more marked decrease (62%) as compared to the controls (36%). It is conceivable that the patients experienced more anxiety than the controls and therefore, it may be argued that the more marked decrease in CBV in patients may be due to anxiety related cerebral vasoconstriction. Unfortunately, the investigators did not report levels of state anxiety and CO₂ and no firm conclusions are possible (Mathew, 1993).

Lactate infusion is a well known panic inducing technique (Gorman, 1987). Lactate also reduces brain P^H and increases CBF. Reiman and associates (1989) found significant increases in CBF bilaterally in temporo-frontal cortex, bilaterally in the insular cortex and the claustrum, bilaterally in or near the superior colliculus, and in or near the left anterior cerebellar vermis during lactate infusion in panic disorder patients. Lactate infusion was not associated with significant changes of regional CBF in non-panicking patients or normals. However, in another study, panic disorder patients who panicked during lactate infusions showed smaller increases or decreases in CBF as compared to the others (Stewart et al, 1988). Yohimbine is also known to precipitate panic attacks in predisposed individuals. Yohimbine decreased bilateral frontal cortical blood flow (relative to the rest of the brain) consistently, in comparison to a placebo, in panic disorder patients but not in control subjects (Woods et al, 1988).

Most studies on pharmacologically induced anxiety showed reduced CBF with severe anxiety. Regional variations in the cerebral vasoconstriction related to severe anxiety are unclear.

EXPOSURE OF PHOBIC OBJECTS

Behavioral techniques for anxiety induction represent 'cleaner' anxiety induction. Exposing patients with phobias to the fear inducing object or situation would seem to be an effective anxiety inducing behavioral technique. In one such study,

patients with 'contamination fear' were exposed to a contamination object through imageries and in vitro exposure. In vitro exposure was associated with significant decreases in global and regional flow values (Zohar et al, 1989). In another study on female patients with animal phobia, patients were exposed to the phobic object. Patients showed lower CBF values when they were exposed to the phobic object although the difference did not reach statistical significance (Mountz et al, 1989).

Other investigators (Wik et al, 1993) measured CBF with PET in volunteers with snake phobia during exposure to the phobic object. The visual stimulation presumably increased CBF in the occipital cortex (sensory stimulation?) but flow was reduced in the hippocampus, orbito-frontal, prefrontal, temporal and posterior cingulate cortex. These studies also indicate an anxiety related cerebral vasoconstrictive factor. Once again, they do not provide any meaningful insights into regional variations.

OTHER RELEVANT STUDIES

CMR glucose measured with PET during dreams showed positive correlations with anxiety in lateral parietal and medial frontal cortex and negative correlations in adjacent white matter (Gottschalk et al, 1991). In another PET scan study of CMR glucose during an active vigilance task, activation of basal ganglia metabolism was seen. Benzodiazepine therapy resulted in reduced metabolism of cerebral cortex, limbic system and basal ganglia. Basal ganglia was identified as a brain region very relevant to anxiety (Wu et al, 1991). Yoga meditation did not produce any significant changes in CMR glucose; however, the frontal-occipital ratio significantly increased suggesting increased frontal activation (Herzog et al, 1990).

CBF/CMR IN OBSESSIVE COMPULSIVE DISORDER

Functional brain imaging studies were performed by a number of investigators on patients with OCD. This line of investigation was complicated by a number of factors. Obsessive compulsive disorder has a wide variety of clinical manifestations. In addition, these patients vary in degrees of associated anxiety and depression. Some of the available studies focused primarily on regional as opposed to global CBF and CMR. Different imaging techniques were utilized and because of the differences in the data they produced, comparisons between studies

were difficult. In spite of these difficulties, the investigators have come up with meaningful results which were replicated several times. Phobias are sometimes classified under obsessive compulsive disorder. CBF/CMR studies on phobic subjects were reviewed above.

Several CBF studies in OCD were performed with HMPAO-SPECT. In one study, when ten non-depressed, medication free OCD subjects were compared to eight matched controls, patients had higher medial frontal flow. Anxiety in these patients significantly correlated inversely with CBF (Machlin et al, 1991). Treatment with fluoxetine over three to four months showed decrease in medial frontal cortical CBF (Hoehn-Saric et al, 1991). In another study with the same CBF measurement technique, patients showed increased flow to orbital cortex bilaterally, left postero-frontal cortex and bilateral high dorsal parietal cortex. CBF was decreased in the caudate bilaterally. When CBF was measured with ¹³³Xenon, increase in OCD symptoms produced by m-chlorophenylpiperazine (a serotonin agonist) correlated significantly with CBF, especially in the frontal lobes (Hollander et al, 1991).

Studies of CMR glucose in OCD patients were performed with PET by several investigators. In OCD patients, CMR was significantly elevated in the left orbital gyrus and bilaterally in the caudate in comparison to normals and depressives. Left orbital gyrus CMR was increased significantly and right orbital gyrus non-significantly in OCD in comparison to the other two groups. Successful treatment did not alter this finding. Caudate CMR increased with treatment with a number of drugs in responders but not in non-responders (Baxter et al, 1987). The same investigators performed a second study with improved methodology. CMR glucose for the entire cerebral hemispheres, heads of the caudate and orbital gyri were higher in patients with OCD as compared to normal controls. Both left and right orbital gyri showed significant elevations in patients (Baxter et al, 1988). Nordahl and associates (1989) compared eight non-depressed OCD patients with thirty normal volunteers. Orbital CMR was high in OCD patients; however, caudate metabolism was same in patients and controls. Right parietal and left occipital-parietal regions were higher in normals than in the patients. The investigators did not study whole brain CMR.

Swedo and associates (1989) studied CMR glucose with PET in nine men and nine women with childhood onset OCD. The OCD group showed in-

creased CMR glucose in left orbital and right sensorimotor regions and bilaterally in anterior cingulate gyri and prefrontal areas. Ratios of regional to mean cortical CMR were increased for the right prefrontal and left anterior cingulate regions in the patient group. A significant correlation was observed between right orbital CMR and OCD severity. Six patients who failed to respond to clomipramine had significantly higher right anterior cingulate and right orbital CMR as compared to the responders. State anxiety during CMR measurement correlated significantly with right prefrontal, left prefrontal and right orbital CMR expressed as ratios to the mean cortical CMR. OCD patients who panicked during the scan revealed significantly lower left premotor CMR and higher right prefrontal CMR; the latter was expressed as a ratio to mean cortical CMR.

Martinot and associates (1990) found results quite different from the other studies. They found lower CMR glucose in all brain regions in sixteen OCD patients as compared to eight controls. Lateral prefrontal cortex (expressed as a ratio to global CMR) was significantly lower in OCD patients. No abnormalities were found in orbital CMR. Another CMR glucose study was performed on ten OCD patients with depression, twelve OCD patients without depression, six manics, ten unipolar and ten bipolar depressives and twelve controls. OCD with major depression was distinguished from the non-depressed OCD state by decreased left dorsal anterolateral prefrontal glucose metabolic rates. Lower CMR in left dorsal anterolateral prefrontal cortex characterized unipolar and bipolar depressives as well (Baxter et al, 1989).

Benkelfat and coworkers (1990) examined CMR glucose in eight OCD patients after an average of sixteen weeks of treatment with clomipramine. Regardless of the change in clinical status, CMR decreased in orbital cortex and left caudate significantly. Right anterior putamen showed increase in CMR. Good responders showed significantly more marked decrease in left caudate than non-responders. No other brain region showed any significant change. CMR glucose measurements were repeated in thirteen OCD patients by Swedo and associates (1992), after clomipramine, fluoxetine and no drugs after an average of twenty months. In responders, orbito-frontal CMR (expressed as a ratio to global CMR) decreased significantly on both sides. Among the treated patients, the right orbitofrontal metabolism decrease correlated with two

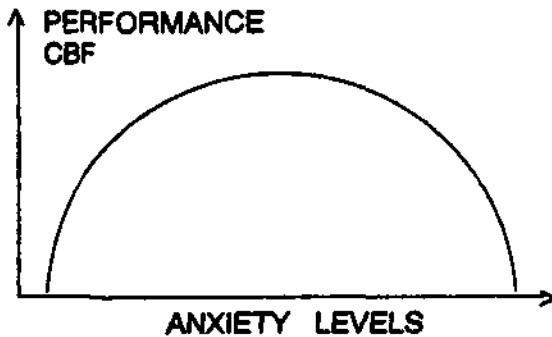
measures of OCD improvement. Baxter and colleagues (1992) studied ten OCD patients before and after treatment with either fluoxetine alone or behavioral treatment. In both groups, right caudate CMR decreased significantly in treatment responders but not in non-responders. Percentage change in right caudate CMR correlated with percentage change in the obsessive compulsive disorder severity significantly in the fluoxetine group and non-significantly in the behavioral therapy group. Right anterior cingulate gyrus and left thalamus decreased with fluoxetine but not with behavioral modification (Baxter et al, 1992).

Azari and associates (1993) performed a multiple regression / discriminant analysis of CMR glucose in ten OCD patients before and during pharmacotherapy. Before therapy, a discriminant function reflecting parietal, sensory-motor and mid-brain CMR glucose interdependencies correctly classified eighty percent of the patients; after therapy seventy percent were classified as controls, most of whom were responders. Before therapy, CMR glucose interdependencies involving basal ganglia, thalamus, limbic and sensory and association cortical regions distinguished sixty seven percent of responders and seventy five percent of non-responders. After therapy, all responders were classified as controls; classification of non-responders remained unchanged.

Horwitz and associates (1991) computed correlations between regional CMR in eighteen OCD patients. The two regions that had the largest number of correlations that differed significantly between groups (OCD patients and controls) were left hemisphere superior parietal region and left hemisphere anterior medial temporal area including amygdala. Correlations involving the caudate did not differ between the groups for most part. Anterior limbic / paralimbic regions had correlations in the OCD group that were significantly larger with frontal areas than in controls, and correlations that were significantly smaller with posterior brain regions. This pattern was especially pronounced for the left hemisphere anterior medial temporal regions.

Patients with obsessional slowness exhibit extreme slowness in the execution of some everyday tasks such as washing and eating. This may be due to time consuming rituals, checking behavior and compulsions. Sawle and associates (1991) studied six patients with obsessional slowness with PET-CMR oxygen (regional cerebral oxygen metabolism) and presynaptic nigrostriatal system integrity.

Figure 3
The Inverted U relationship between levels of anxiety, performance and CBF



Optimum performance occurs with moderate anxiety levels, less or more anxiety cause deterioration. Mild anxiety is also associated with CBF increase, with more severe anxiety being associated with CBF decrease. Thus, there seem to be inverted U relationships between anxiety and both performance and CBF.

The findings were of focal hypermetabolism in orbital frontal pre-motor and midfrontal cortex while dopa (^{18}F -dopa) uptake into caudate, putamen and medial frontal cortex was normal. More recently, Rauch and coworkers (1994) provoked obsessions in eight OCD patients with appropriate stimuli during CBF measurement with PET. OCD symptom activation resulted in significant increases in CBF to left anterior cingulate and bilateral orbito-frontal cortex.

Trichotillomania (compulsive hair pulling) though classified under "Impulse Control Disorders" in DSM-III-R, resembles OCD to some degree. Ten females with this disorder showed a regional CMR glucose pattern very different from OCD patients. Trichotillomania patients showed significantly increased global (grey matter), right and left cerebellar and right superior parietal CMR glucose. However, improvement after clomipramine treatment correlated inversely with anterior cingulate and orbital frontal metabolism similar to the findings from OCD patients treated with the same drug (Swedo et al, 1991).

Results of the CBF/CMR studies mentioned above implicate a wide variety of cerebral structures in OCD. Of the various brain regions identified, orbital prefrontal cortex and to a lesser extent, the caudate stand out. OCD seems to be associated with increased CMR glucose in these two brain regions which return to normality after successful treatment (Baxter, 1992).

CONCLUSION

Different anxiety related factors increase and decrease CBF. Nonspecific arousal mediated by the reticular activating system increase CBF while hypocapnia and sympathetic stimulation decrease CBF. The relationship between CBF and anxiety is complicated by the interplay of these cerebral vasodilatory and vasoconstrictive factors. Under resting conditions, when anxiety related vasoconstrictive factors are not activated, CBF seems to be highest in the frontal regions. Mild increases in arousal increase CBF globally and in the frontal regions, bilaterally. The same effect is seen with mild anxiety. More severe anxiety seem to be associated with CBF decrease. It must be noted that these findings of CBF increase during mild anxiety and decrease during severe anxiety are supported by many, but not all studies.

CBF increase during mild anxiety is easy to explain on the basis of reticular activating system mediated arousal. Increase in brain activity is associated with parallel increases in CBF and CMR. CBF reduction during severe anxiety is more difficult to explain. Hypocapnia would seem to be the most likely explanation; however, several studies in which CO_2 was measured and controlled for, could not explain the reduction in CBF on this basis.

Anxiety related increase in sympathetic cerebral vasoconstrictive tone is another factor to be considered. Anxiety disorder patients have been shown to have higher sensitivity to sympathetic activation (Nesse et al, 1984). Thus, it would seem highly likely that sympathetic activation is the vasoconstrictive factor associated with severe anxiety. Sympathetic activation may also explain cerebral ischemic events associated with anxiety and panic (Coyle & Serman, 1986; Mathew et al, 1987). Over sensitivity to sympathetic stimulation has been implicated in cerebral vasospasm associated with subarachnoid hemorrhage (Boullin, 1980; Rosenblum & Guilianti, 1973).

According to the Yerkes-Dodson Law, "The optimum level of aversive stimulation in the control of learning is at some moderate intensity, lower and higher values being less effective; the optimum level decreases as task complexity increases" (Yerkes & Dodson, 1980; Hilgard et al, 1971). This would seem to indicate that moderate levels of anxiety facilitate performance, with higher levels having the opposite effect. More recent psychophysiological experiments provided partial support for this inverted U relationship (Figure 3) between anxiety and performance (Duffy, 1972). A similar inverted U relationship between anxiety and CBF/CMR is of considerable heuristic significance.

However, it must be pointed out that a number of mechanisms protect the brain from anoxia and that the CBF has to fall below 20ml/100gm/minute for ischemic symptoms to occur (Lassen & Astrup, 1987). Nobody has reported CBF below this level, even in severe anxiety. However, it must also be noted that panic attacks were associated with focal cerebral ischemia; unfortunately CBF measurements were not available in studies by Coyle and Serman (1986) and Mathew and associates (1987).

There is not enough information to justify firm conclusions about the effects of anxiety and panic on flow and metabolism in different brain regions. Study of regional CBF and CMR is plagued by a number of technical problems. First of all, even the best currently available imaging techniques do not have the spacial resolution necessary to image small sub-cortical structures satisfactorily. Many of the studies were performed with techniques with poor spacial resolution. Identification of sulci which is necessary for the separation of cortical regions can be very difficult on tomographic slices. Most studies did not have the statistical power (number of participants) necessary to identify regional differences. More studies with high resolution techniques need to be conducted with larger numbers of participants.

As was pointed out earlier, many CBF techniques do not provide absolute values; flow is approximated from the intensity of radioactivity registered from different brain regions (count rates). The assumption is that count rates represent the amount of radioisotope (tracer) delivered to that region via the blood circulation and therefore, they serve as an indices of blood flow. However, count rates will also be influenced by quantity of isotope injected, extravasation at the injection site, total blood volume, ratio of flow to the brain as compared to other tissues, blood brain partition coefficients,

proximity of the region to the scintillation detector, intervening tissues between the region and the scintillation detector, etc. Regional count rates are expressed as a ratio of count rates from another region (reference region) or the entire brain.

This approach rests on the assumption that the "reference brain region" will not show (anxiety related) CBF changes and that in that region, flow will remain stable across different measurements. Since anxiety is likely to change both regional as well as global CBF/CMR through a variety of mechanisms, circulation in no region (or the entire brain) can be considered to be silent during anxiety. Thus, the ratio technique is of questionable validity, especially in anxiety research. The assumption that regional flow (as opposed to global flow) is mainly an index of brain function is also weak. It also needs to be pointed out that sympathetic innervation of cerebral blood vessels show regional variations. Sympathetic stimulation has also been shown to influence CMR (Edvinsson et al, 1993).

There seems to be general agreement that OCD may be associated with increased CBF and CMR in orbital frontal gyrus and perhaps, in the caudate. There is less agreement about the involvement of other brain regions. The effects of anxiety and depression of CBF/CMR in OCD patients deserve further study.

Most of the available reports on CBF/CMR and anxiety are from normals, panic disorder patients and OCD patients. Patients with other anxiety disorders have not been studied. In all probability, like OCD, other anxiety disorders may also be associated with specific regional abnormalities in CBF and CMR.

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