BIOCHEMICAL FACTORS IN ANXIETY AND RELATED DISORDERS

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general metabolism of cells, has proved to be of such significance to the pharmacologist, the biochemist, the neurologist, and possibly, to the psychiatrist'' (1957).

The investigation of serotonin's role in anxiety has centered on the heterogeneous and complex nature of the various serotonin receptor sites and serotonin re-uptake sites in both normal and abnormal brains as well as the effects of various serotonin agonists and antagonists. There are currently seven different serotonin receptor sites that have been identified and located in a variety of pre- and postsynaptic sites throughout the brain (Gonzalez-Heydrich & Peroutka, 1990). These seven receptors are broken into three classes: 5-HT_1 class (5-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D}), 5-HT class (5-HT_{1C} 5-HT_{2A}, and 5-HT_{2B}), and the 5-HT, class (5-HT_1). 5-HT_{lc} is grouped in the 5-HT_2 family because of its similarities to the 5-HT_{2A} and 5-HT_{2B} subtypes. It is expected that this list will expand in the future.

To complicate things further, different second messenger systems have been associated with different serotonin receptors (Gonzalez-Heydrich & Peroutka, 1990). All of this helps explain the seemingly conflicting data obtained from various animal and human studies involving serotonin.

Recent studies of the anxiety disorders (obsessive-compulsive disorder, panic disorder, and generalized anxiety disorder), have implicated the

involvement of serotonin. This common factor is remarkable when compared to the distinct signs and symptoms of these disorders as categorized in the DSM-III-R. 5-HT selective drugs such as 5-HT releasing agents (e.g., fenfluramine) and 5-HT receptor agonists (e.g., metachlorophenylpiperazine [*m*-CPP], buspirone) have distinguished anxiety disorders in terms of behavioral and neuroendocrine responses. Fenfluramine by itself had minimal behavioral effects in obsessive-compulsive disorder (OCD) patients but produced panic episodes in panic disorder (PD) patients (Murphy & Pigott, 1990).

m-CPP produced changes in neuroendocrine responses as well as behavioral differences among various psychiatric patient groups as well as when compared to control groups. Some of the anxiety related responses could be differentiated depending on the dosage and route of administration of *m*-CPP.

When obsessive-compulsive disorder patients were given oral *m*-CPP, they showed transient exacerbations of their obsessive-compulsive symptoms while normal controls had no response (Zohar, Mueller, Insel, Zohar-Kadouch, & Murphy, 1987). This exacerbation of symptoms occurred in 11 of 12 OCD patients. Also notable is that a number of these affected patients reported the emergence of new symptoms or symptoms that had not been present for many months. A review of a number of studies using *m*-CPP

showed that panic symptoms could be significantly increased in PD patients at oral doses of 0.25 mg/kg and in OCD patients at oral doses of 0.5 mg/kg while in healthy volunteers minimal anxiety symptoms occurred with 0.5 mg/kg (Zuardi, 1990).

Cortisol level responses to intravenous and oral doses of *m*-CPP are different between PD patients and OCD patients. These in turn are distinct from control group responses (Murphy & Pigott, 1990).

Other evidence for the involvement of serotonin includes the actions of psychopharmacological agents used to treat anxiety disorders. Of the tricyclic antidepressants, clomipramine has shown a significantly greater ability to stop the re-uptake of 5-HT into brain synaptic terminals. In the treatment of OCD. clomipramine has proven superior to other tricyclics and monoamine oxidase inhibitors in numerous studies (Murphy & Pigott, 1990). Another 5-HT re-uptake blocker, fluoxetine, is also very effective in treating OCD.

The mechanism of action of agents like clomipramine and fluoxetine in blocking 5-HT re-uptake is not well understood. It is thought not to be related to the specificity of action of the agent on serotonin transport after acute administration of the agent but rather to adaptive changes in these sites following chronic administration (Leonard, 1988). This stands in contrast to GABA-mediated agents such as benzodiazepines that show reduction in

anxiety within hours after intake. 5-HT_{IA} receptor agonists are currently being established as effective tools to treat GAD. Again, the mechanism of action is not clearly identified. Agents such as buspirone act as agonists on presynaptic 5-HT_{1A} receptors but are also partial agonists at the postsynaptic 5-HT_{1A} receptor (Eison, 1990). An important distinction between these 5-HT_{1A} agonists and the previously discussed serotonin re-uptake blockers is that the 5-HT_{1A} agonists act specifically at 5-HT_{1A} while the re-uptake blockers make serotonin available to interact with all subtypes of 5-HT receptors (Eison, 1990).

Buspirone has been shown to be as equally effective in treating generalized anxiety disorder as benzodiazepines (e.g., diazepam). Two significant differences should be noted. First, benzodiazepines work after the first dose while buspirone takes weeks of administration to get a similar result. Two, the side effect profile of buspirone does not include sedation, ataxia, amnesia, and withdrawal problems that can be associated with benzodiazepines (Charney, Krystal, Delgado, & Heninger, 1990). Clinical indications for using buspirone in GAD include patients who are elderly, have concurrent medical problems, show mixed symptoms of depression and anxiety, and those who do not demand immediate gratification or the immediate relief they associate with a benzodiazepine response (Rickels, 1990).

The 5-HT_2 receptor is also being studied because various 5-HT_1 receptor antagonists, such as ritanserin, have been effective in GAD (Charney, Krystal, Delgado, & Heninger, 1990). Early animal studies looking at 5-HT_3 receptor antagonists indicate it may have anxiolytic properties (Jones et al., 1988).

GABA/BENZODIAZEPINE RECEPTOR COMPLEX

Gamma-aminobutyric acid (GABA) is an amino acid neurotransmitter in the CNS which, as the most important inhibitory neurotransmitter, is potent in its ability to affect neuronal discharge. There are two subtypes of GABA receptors: GABA-A receptors where benzodiazepines enhance the binding of GABA, and GABA-B receptors where benzodiazepines do not enhance the binding of GABA (Wojcik & Neff, 1984). Currently, the most predictable anxiolytic effects are associated with the benzodiazepines, which facilitate the activity of GABA. The benzodiazepines diazepam and alprazolam have been widely prescribed for generalized and anticipatory anxiety, and panic disorder (Rickels, Schweizer, Csanalosi, Case, & Chung, 1988; Sheehan, 1987), respectively. Such linkage between the GABA-ergic subsystem and specific benzodiazepine receptors has provided a molecular basis of anxiety and understanding the neurobiology of anxiety. Presently, there are two receptor hypotheses for the genesis of anxiety. The first one is that changes in activity of endogenous ligands for the benzodiazepine receptor (e.g., an excess of

anxiogenic) or a deficiency of anxiolytic substances regulates anxiety. The second one is that shifts in the benzodiazepine receptor sensitivity (e.g., increased or decreased receptor sensitivity to agonist drugs) may regulate anxiety (Nutt, Glue, & Lawson, 1990).

In 1977, two independent groups of researchers in Denmark and Switzerland reported the existence of saturable, high affinity, and stereospecific binding sites for benzodiazepines in the CNS of reptiles and mammals (Mohler & Okada, 1977; Squires & Braestrup, 1977). The highest concentrations of benzodiazepine receptors are found in the cerebral cortex, cerebellum, and amygdala, and lesser concentrations in the hippocampus, striatum, and spinal cord (Braestrup, Albrechtsen, & Squires, 1977). Studies exploring the relationship between the GABA-ergic system and benzodiazepines have substantiated the presence of a pharmacologic receptor for benzodiazepines in brain.

Benzodiazepines potentiate the effects of GABA, but do not produce anxiolysis when GABA is absent (Guidotti, 1981). Activation of benzodiazepine binding sites causes an allosteric change in the GABA receptor recognition site, consequently increasing receptor sensitivity to GABA (Enna, 1984; Paul & Skolnick, 1983; Tallman, Thomas, & Gallager, 1978; Tallman, Paul, Skolnick, & Gallager, 1980). Small permeable anions such as chloride also increase the binding of GABA to their receptors (Costa,

Rodbard, & Pert, 1979). These two effects combined suggest that GABA inhibits neuronal excitability by opening the chloride channel ionophore directly linked to GABA receptors. Consequently, chloride conductance increases and allows chloride ions to move more readily from the extracellular space to the inside of the neuron (McDonald & Barker, 1979). Therefore, a structural and functional model of the GABA/Benzodiazepine receptor "supramolecular receptor complex" consisting of a chloride ion channel and two binding sites has been formulated. One receptor site binds GABA and the other one binds benzodiazepine (Breier & Paul, 1990). Barbiturates also enhance the GABA receptors by interacting directly with the chloride channel (Enna, 1984).

It has been proposed that hyperexcitability of certain neuropathways is associated with anxiety. In an overactive state, a feedback signal to a GABA neuron is sent and then GABA is released into the synaptic cleft. GABA binds to its receptor to open chloride channels and increase the influx of chloride ions into the neuron. The net effect of enhanced chloride permeability causes hyperpolarization of the nerve membrane. Hyperpolarization makes the neuron less likely to be excitable and this is associated with the alleviation of anxiety. With the administration of a benzodiazepine, GABA-mediated chloride conductance is facilitated and excitability of the neuron is further inhibited (Goldberg, 1984).

Isotope-labeled ligands of benzodiazepine receptors have been used to explore the neurochemical basis of epileptic patients: indirect evidence for the role of the GABA/benzodiazepine receptor in the pathophysiology of anxiety has been found (Savic et al., 1988).

Reduced benzodiazepine sensitivity was reported through a study in response to intravenous administration of diazepam. Saccadic eye movement velocity decreased less in patients with panic disorder than in nonanxious control subjects and suggests that panic disorder is associated with a functional subsensitivity of the GABA/benzodiazepine supramolecular complex in brainstem areas controlling saccadic eye movements (Roy-Byrne, Cowley, Greenblatt, Shader, & Hommer, 1990). The reason for the reduced sensitivity is not clear but may be related to the anxiety disorder or may be related to the effect of benzodiazepine (Hoehn-Saric, 1991).

Under stressful conditions, the secretion of steroid hormones such as progesterone and deoxycorticosterone will increase and significantly affect the CNS function. Their metabolites have potent benzodiazepine like effects that mediate through recognition sites on the GABA/ benzodiazepines receptor (Breier & Paul, 1990).

Data from the use of β-carboline-3-carboxylate ethyl ester ((β-CCE) supports the role of the GABA receptor in mediating anxiety. β-CCE, a

benzodiazepine receptor antagonist, has been used to probe the neurobiological base of anxiety (Braestrup & Nielsen, 1981). Administration of β-CCE to rhesus monkeys and a β-carboline derivative, FG-7142, to humans induced behaviors similar to the stress-related responses of behavioral "agitation" accompanied by marked physiologic and endocrine changes. Administration of a benzodiazepine then blocks such responses (Dorow, Horowski, Paschelke, Amin, & Braestrup, 1983; Insel et al., 1984).

At present, the activation of a GABA-ergic subsystem has the most predictable anxiolytic effects (Hoehn-Saric, 1982). More sophisticated research in this area has been carried out and will eventually lead to a better biochemically based explanation into the genesis of anxiety disorders in the future.

OTHER BIOCHEMICAL MEASUREMENTS IN ANXIETY

Lactic Acid (Lactate)

Higher blood concentrations of lactate were found in anxiety-prone individuals than in normal individuals after exercise (Linko, 1950). Pitts and McClure (1967) and other researchers (Gorman et al., 1988, 1989) intravenously infused lactate solution, anxiety symptoms were provoked only in susceptible individuals. This precipitation can be successfully inhibited or

attenuated by the administration of tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs), but not by benzodiazepine or β-adrenergic antagonists (e.g., propranolol) (Liebowitz et al., 1984). Although the mechanism for lactate's effect is not clearly understood, it may be related to the rise in the lactate-pyruvate ratio, lowering the level of ionized calcium, and the concomitant fall of intraneuronal pH in the chemoreceptor (Carr & Sheehan, 1984). The biochemistry of these chemically induced anxiety symptoms still needs to be studied further (Gaffney, Fenton, Lane, & Lake, 1988; Gorman et al., 1989; Reiman et al., 1989).

Carbon Dioxide

The investigation of carbon dioxide's role in causing anxiety remains confusing and perplexing to researchers. Carbon dioxide levels are adjusted acutely through a person's respiratory rate. Increasing an individual's breathing rate (hyperventilation) leads to hypocapnia (reduced carbon dioxide in the circulating blood) while decreasing the breathing rate (hypoventilation) leads to hypercapnia (elevated carbon dioxide in the circulating blood). Investigators have used this phenomenon as well as exposing patients to predetermined concentrations of carbon dioxide to accurately measure its effect on anxiety, especially panic attacks.

One initial proposal was that alterations in blood carbon dioxide, which

can have profound effects on cerebral blood flow, caused anxiety. However, repeated studies have shown that hypercapnia and hypocapnia have opposite actions on blood flow but both are anxiogenic (Nutt, 1990). The possibility that marked hyperventilation seen in compensation to hypercapnia as the cause of panic has also been discredited.

Another hypothesis involves carbon dioxide induced stimulation of noradrenergic neuronal function leading to panic attacks. Although animal studies have shown evidence for this, it has not been replicated in human studies (Woods, Charney, Goodman, & Heninger, 1988). Along these lines, one recent study has implicated hyperventilation to increased vagal tone and subsequent reduced parasympathetic nervous system activity. This would result in a relative increase in sympathetic activity without direct sympathetic excitation (George et al., 1989).

A combination cognitive-physiological model has also been suggested. Hyperventilation or hypoventilation induces body sensations that are perceived as unpleasant and are interpreted in a catastrophic manner. This would account for the paradoxical anxiogenic effect of both hypo- and hyperventilation. Also, this is consistent with studies showing evidence for behavioral hypersensitivity to carbon dioxide and weak or no evidence for physiologic hypersensitivity to carbon dioxide in patients with panic disorders (Woods, Charney, Goodman, & Heninger, 1988).

Caffeine

Because it is thought to have stimulant actions that could elevate mood, decrease fatigue, and increase capacity to work, caffeine is a popular ingredient in a variety of drinks, foods, and medications (Rail, 1990).

Caffeine is found mostly in drinks such as coffee (90 mg to 125 mg/ 250 ml), tea (40-60 mg/ml), cola drinks (40 mg/330 ml), and hot chocolate (5 mg/225 ml). Foods with coffee or chocolate also contain caffeine. Chocolate bars have about 20 mg per small bar. A significant number of over-the-counter preparations for analgesia, coughs, colds, and asthma also contain caffeine (Bruce, 1990). It is estimated that 80% of the world's population consumes caffeine. The per capita consumption among American adults is about 200 mg per day (Jaffe, 1990).

Caffeine is a methylxanthine and is similar in structure to xanthine, theophylline, and theobromine (Rail, 1990). As a central nervous system stimulant, caffeine's biochemical action is thought to be mediated by blocking receptors for adenosine (Boulenger, Patel, & Marangos, 1982). Caffeine does cause increased cerebrovascular resistance with resultant reduction in cerebral blood flow (Rail, 1990). However, attempts to correlate this specific action to caffeine's anxiogenic properties has been unsuccessful (Mathew & Wilson, 1990).

The clinical presentation of caffeine-induced anxiety can mimic other anxiety disorders such as PD and GAD (Charney, Heninger, & Breier, 1984). The DSM-III-R lists three criteria for the diagnosis of caffeine intoxication. One, the recent consumption of caffeine, usually more than 250 mg. Two, at least five of the following signs: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of inexhaustibility, or psychomotor agitation. Three, that the anxiety is not due to any physical or other mental disorder. Thus caffeine toxicity can be difficult to distinguish from other anxiety disorders unless an accurate history is obtained or toxicology tests are ordered.

In addition to appearing similar to other states, caffeine is known to complicate and worsen the conditions of persons with a pre-existing anxiety disorder. This has been noted in the clinical observation that many panic patients will put themselves on a caffeine-free diet because the subjective effects of caffeine (arousal, insomnia, upset stomach, and tremor) are unpleasant (Nutt, 1990).

In one study, patients with either generalized anxiety or panic disorders who underwent caffeine abstinence showed a significant reduction in long-standing anxiety symptoms as well as reductions in their anxiolytic medications. Some of these patients consumed less than 200 mg of caffeine a

day prior to abstaining, thus illustrating the powerful effect of even low doses of caffeine (Bruce & Lader, 1989).

Caffeine is also associated with a withdrawal syndrome. Headache and fatigue are the most frequently listed symptoms along with anxiety, impaired performance, nausea, and vomiting. The onset is 12 to 24 hours with a peak at 20 to 48 hours and lasting up to one week. Thus patients wishing to abstain from caffeine should be advised of the short-term withdrawal symptoms and high users of caffeine should taper their intake over one to two weeks to minimize these symptoms (Bruce, 1990).

Miscellaneous Biochemical Measurements

Other studies suggest certain physiological differences between individuals with and without anxiety. Individuals with anxiety disorders show an increased resting forearm blood flow (Kelly & Walter, 1968), brisker deep tendon reflexes, and an elevated resting pulse-rate (Claycomb, 1983). They can also be more sensitive to various types of painful stimuli, have a low exercise tolerance, and experience spontaneous fluctuations of galvanic skin response (Lader, Gelden, & Marks, 1967).

Brain imaging methods, especially positron emission tomography (PET) and single photon emission computerized tomography (SPECT) have been used to study blood flow, oxygen consumption, and receptors (Sadzot, Frost,

& Wgner, 1989; Innis et al., 1989). During an anticipatory anxiety state, activity in the bilateral temporal poles increased. They also occurred in lactate-induced anxiety states. These findings suggest that anxiety state is related to the function of the temporal cortex (Reiman, Fusselman, Fox, & Raichle, 1989; Reiman et al., 1989).

CONCLUSION

The pathophysiology of anxiety most likely involves the interactions between different brain neuronal systems. The GABA-ergic system associated with benzodiazepine receptors, the noradrenergic (NA) systems and the serotonergic systems are definitely involved in the biochemistry of anxiety. An interaction between the NA system and GABA/Benzodiazepine receptor system has been proposed (Redmond & Huang, 1979), and serotonin has been proposed to be involved in the anxiolytic properties of benzodiazepine (Paul, Marangos, & Skolnick, 1981). Insel, et al., (1984) suggested that there are two different neuropharmacological models of anxiety: NA and GABA-ergic pathways. The GABA-ergic system corresponds to “fear or conflict” or “psychic” manifestations of anxiety that often require benzodiazepine treatment. The NA activation corresponds to “alarm” or “autonomic” manifestations of anxiety such as panic attacks and these respond favorably to tricyclic antidepressant therapy. Anxiety induced by yohimbine, a noradrenergic a-2 receptor antagonist, has been successfully attenuated by

alprazolam, a triazolobenzodiazepine. This suggests that a yohimbine-induced anxiety state may be related to both NA and GABA activities (Charney, Breier, Jatlow, & Heninger, 1986). Also, other data suggest that the serotonergic pathway is involved in anxiety. At present, the role of other neurotransmitters such as acetylcholine, dopamine, histamine, adenosine, and neuropeptides, is not well understood; it appears to be minimal (Hoehn-Saric, 1982).

Of all the discussed hypotheses and methods for exploring the biochemistry of anxiety disorders, none is without flaws. As research activities continue, certain subtypes of pathological anxiety will be better understood by applying certain biochemical paradigms. These models can also help clinicians to identify specific biological etiologies for their patients which will promote an accurate diagnosis and effective treatment.

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