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PSYCHOBIOLOGY AND THERAPEUTIC APPROACHES TO ANXIETY STATES

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SUMMARY

The current psychobiology and the therapeutic principles of anxiety states have been reviewed. The septo-hippocampal system probably operates as the organ of match-mismatch comparator. A dysfunction of this internal comparator could possibly be the source of anxiety. There seem to be two distinct psychobiologic models for panic disorder and chronic anxiety state. The therapeutic responses of panic disorder to TCA and MAOI and the response of the chronic anxiety state to benzodiazepines supports the classification of two distinct syndromes. However different provocative challenge tests have not clearly delineated the role of nor-adrenergic (NE) mechanisms in panic disorder and benzodiazepine receptor theory for chronic anxiety state. Challenge tests with receptor specific pharmacologic agents may reveal the molecular basis of these disorders unlike the tests with non-specific agents like lactate and caffeine.

Introduction

The phenomenon of anxiety is universal to conscious existance. It is closely linked to fear in the phylogenetic evolution of affects. Like any other affect, it is best expressed in human beings. A variety of stressful life situations may bring about anxiety. Anxiety may be considered as a physiological reaction to stress. In the domain of stress adaptive reactions it bifurcates to fear, rage or withdrawal. Hence, it could be considered as a very primary affect precondition to life.

A quantitative or qualitative deviation from normal stress anxiety relation may be viewed as a formal definition of clinical or pathological anxiety. There are various discriptive and phenomenological models of anxiety and its subtypes. These do not fall into the purview of the present paper. It is pertinent to mention that in all experimental studies, only the somatoautonomic component is considered to be identical to manifest anxiety. It is more appropriate to confess that the important and fundamental "psychic" component of anxiety is closely linked to ontogeny of mind and consciousness and remains beyond the scope of present day Biology. Therefore, only a modest attempt is made to understand the neuro biologic substrate of anxiety and principles of Pharmaco-therapy.

Neurobiologic Substrates of Anxiety

It has been estimated that at least 2-5% suffer from anxiety disorders in the general population and the morbidity associated with it is about 75%. There have been various objective and psycho-physiologic measurements of anxiety in last 20 years (Granville-Grossman 1971). These are of value in assessing anxiety, but of little theoretical significance. There appears no psychophysiologic or biochemical measure that is specific to this illness (Lader 1972, Tyrer and Lader 1976). During last decade, advances in basic neurosciences and experimental clinical researches (by the use of provocative (challenge) tests) have implied the role of NE (norepinephrine), benzodiazepine receptors, endogenous opiates, purines and GABA (gamma aminobutyric acid) in the cause and treatment of anxiety (Braestrup and Nielsen 1983, Redmond 1979, Tallman et al. 1980, Phillis and Wu 1981). The neural substrates like amygdaloid nucleus, medial dorsal nucleus of thalamus, posterior hypothalamus, mamillary body and the septohippocampal system have been implied to generate and express anxiety. The septohippocampal system probably operates as

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the organ of hesitation and doubt by the process of match-mismatch comparison (Shaw et al. 1982). It is the basis of conflict-punishment paradigm in the evaluation of anxiolytic drugs and could possibly be the sheet of anxiety if it becomes overactive.

Pharmacologic models of anxiety

The Pharmacologic models of anxiety and panic disorders are based on the therapeutic considerations and the challenge tests conducted with the use of (DL)-Lactate, yohimbine, isoproterenol and other agents. Selective benzodiazepine receptor blockers have been used as 'challenge agents' in volunteers. The sodium lactate infusion elicits panic reactions that are claimed to mimic natural panic attacks in susceptible persons (Gorman et al. 1985, Liebowitz et al. 1984). Following treatment by MAOI (Monoamine oxidase inhibitors) or TCA (Tricyclic antidepressants) the lactate response turns to control levels (Kelly et al. 1971). The lactate model suggests the involvement of underfined regulatory abnormalities. It may be useful in identifying patients responsive to TCA and not be benzodiazepines (Rifkin et al. 1981). There are evidences for hyperactive adrenergic mechanisms in panic disorders. It is seen that imipramine and phenelzine reduce the frequency of panic attacks (Zitrin et al. 1983). Tricyclic antidepressants affecting both serotonergic and nor adrenergic systems are equally effective as antipanic agents. In contrast, the benzodiazepines that are highly effective in treatment of generalised anxiety and nervous disorders do not appreciably alter the course and outcome of panic disorders. Also the treatment of generalised anxiety by TCA appears limited. Down regulation of Beta receptors and up regulation of a_1 receptors occurs with chronic administration of TCA and MAOI (Susler 1981). There occurs also down regulation of a_2 receptors by some TCA and MAOI drugs (Charney et al. 1981) Beta receptor down regulation appears to be linked to a general effect of antidepressive therapies, but it is not yet clear which effect is possibly linked to antipanic activity. However, TCA and MAOI reduce NE turnover and yohimbine that produces panic attack by its a_2 antagonism, increases NE turnover. Chronic alprazolam and imipramine administrations and yohimbine challenge also suggest the role of a_2 receptors in panic disorders (Charney et al. 1984 1985). Buspirone, a non benzodiazepine anxiolytic that increases locus ceruleus firing does not have a satisfactory explanation on its mechanism of action (Sangera et al. 1983). Therefore, a reduced a_2 autoreceptor sensitivity, increased activity of excitatory inputs or reduced inhibitory input may lead to the common manifestation of increased NE turnover in anxiety and panic states. The reduction of a_2 receptors by imipramine appears contradicting to already reduced a_2 receptor binding in platelets (Vetulani et al. 1980).

The other competitive but not mutually exclusive hypothesis of anxiety is based upon the benzodiazepine receptors which mediate the anxiolytic effect of benzodiazepines by potentiating the inhibitory GABA-ergic mechanism through the effect on a chloride ionophore (Skolnick et al. 1982, Paul et al. 1981). The benzodiazepine receptors have been found in hippocampus, olfactory bulb, thalamic nuclei and cortex and are widely distributed in nature even in schistosomes. The benzodiazepine antagonists (active), Beta carbolines (CCE and FG 7142) are anxiogenic. However, the drug RO-15-1788 though a benzodiazepine antagonist do not possess anxiogenic activity. Therefore, the benzodiazep ine receptors not only mediate anxiolytic effect but may also play a role in generating anxiety

Insel et al. 1984, Ninan et al. 1982, Lippa et al. 1978). There exists a possibility of an endogenous benzodiazepine receptor ligand in the brain. At this time it is not understood how anxiety is related to benzodiazepine receptor-GABA mediated system and its links to nor-adrenergic, enkephalin and serotonergic systems. Molecular pharmacology in future may elucidate the basic mechanisms mediating the anxiety reaction.

Principles of pharmaco-therapy of anxiety states

Various modes of treatments are available for this common disorder like psychotherapies, bio-feedback and meditations. The treatment effects are highly dependent upon personality factors such as suggestibility, level of intellectual sophistication and the individual value systems. Although the efficacy of traditional psychotherapies and modern, fashionable non-pharmacological methods cannot be dismissed, the very unverifiable nature of the process prohibits any scientific enquiry into these methods. Similarly, the undisputed utility of behaviour therapy in circumscribed phobic disorders leads to erroneous generalisation of deconditioning molecular recognisation. Hence it is imperative to restrict the discussion to the principles of current pharmacotherapy of anxiety disorders.

Anxiolytic drugs are substances which reduce pathological anxiety, tension and agitation without therapeutic effect on cognitive or perceptual process. Most of these drugs are also potent anticonvulsants, sedatives and hypnotics. The barbiturates, meprobamates and other non benzodiazepine minor tranquilisers have anxiolytic properties. However, most important group is benzodiazepines which are remarkably non toxic and much less toxic that barbiturates. Meprobamate, much used in 1950's and 1960's but without a known mechanism of action, miscellaneous drugs such as Beta-blockers and some neuroleptics and antidepressants possessing anxiolytic properties, are not usually considered as true anxiolytics. The present day definition of an anxiolytic predominantly rests on anticonflict test. It is a selective action of benzodiazepine receptors and pharmacological specificity of benzodiazepines. Cat muscle relaxation inhibition of pentazole convulsions in mice, inhibition of mouse rotarod performance, inhibition of electric shock induced fighting in mice, inhibition of experimental human anxiety and restoration of behaviour supressed by punishment indicative of anxiolytic effect in man are all correlated with the affinity for these receptors (Baestrup 1981). However, as the neurochemical basis of human anxiety states remains uncertain the recent approaches to pharmacotherapy can be considered empirical in a limited sense.

From the preceding sections it is clear that panic disorders are best treated by TCA, MAOI and the chronic nervous anxiety by benzodiazepines. Beta-blockers can be considered as broad spectrum anxiolytics effective in both panic disorders and chronic anxiety states, however, the response is less pronounced than other agents.

Benzodiazepines

In search for a novel group of CNS acting drugs the 1-4 benzodiazepines were discovered by Sternback and Reeder in 1961 by ring enlargement of biologically inactive quinazoline-N-oxide with methylamine. Thus the 7-chloro-2 methylamino-5 phenyl-3H-1, 4 benzodiazepine-4 oxide-(Chlordiazepoxide) was born and other derivatives followed. For the biologic activity the 1, 4-benzodiazepines ring system, substitution at 7th position,

and phenyl group at position 5 are essential. Roughly all drugs in this class possess anxiolytic, hypnotic, sedative and anticonvulsive properties notwithstanding the fact that they are promoted for different indications. The Pharmacokinetic differences are only important to their clinical activity. Except absorption, all clinical aspects can be correlated to the type of metabolic change the drug undergoes. Chlorazepate and diazepam are rapidly absorbed. Other benzodiazepines are intermediate in time for absorption. Desmethyldiazepam has an average half life of 50 hours. Only 40% of diazepam remains unchanged and otherwise diazepam, chlorazepate, halazepam and prazepam are converted to desmethldiazepam. Therefore, chlorazepate, halazepam and prazepam are just prodesmethyldiazepam which is inturn converted to oxazepam. Chlordiazepoxide is converted to desmethyl chlordiazepoxide – desmethyl medazepam – dismethyl diazepam – demoxapam – oxazepam. Therefore, the drug takes longer time, 2-3 weeks to attain a steady state in slow metabolisers and its effective half life is about 10-40 hours. Drugs like Cimetidine, Disulfiram, Isoniazid and Oestrogens that impair hepatic oxidation can increase plasma levels of these drugs Oxazepam and Lorazepam are directly converted to glucoronic conjugates and are excreted, therefore they have very short half lives. All benzodiazepines have high therapeutic index. Tolerance and dependence to these agents have been demonstrated (Shader 1978, Marks 1978 & Hallister 1978). Physical dependence can develop if excessive dosage of benzodiazepine are used for a long time in patients with unstable personalities. Sudden withdrawal of benzodiazepine that are directly conjugated may result in withdrawal symptoms and rebound anxiety in patient (Fontaine et al. 1985, 1984). Paradoxical reactions, rage reaction, disinhibitions have been reported. Even tolerance to model anxiolytic activity occurs in animals (Stephen and Schneider 1985).

Tricyclic Antidepressants (TCA) and Monoamino Oxidase Inhibitors (MAOI)

More than 60 antidepressant drugs have been marketed since imipramine was first introduced in 1957. In the preceding section it has already been suggested that TCA and MAOI are effective as antipanic agents. Seven double blind trials have compared TCA (imipramine) with placebo in panic disorders and six have shown IMI to be superior to placebo (Marks et al. 1983). Few studies have shown MAOI to be effective in panic disorders (Sheehan et al. 1980). There are evidences that TCA are also effective in generalised anxiety disorder but evidence is not so clear in phobic neurosis (Klein 1974). Abrupt TCA withdrawal may produce symptoms of anxiety (Charney et al. 1980). The effect of new antidepressants on panic disorders is not evaluated. There are now selective MAO inhibitors-clorgyline is MAO-A selective and selegiline is MAO-B selective. Selegiline is marked for dopamine enhancing action in parkinsons disease. The dangerous food and drug interactions characteristic of the other MAOI is not usually found in selective MAO (B) blockers. It appears that only those drugs which are MAO (A) selective carry these risks. The new 5HT selective drug Zimeldine has been withdrawn because of its neurotoxic effects. However, other specific 5HT uptake inhibitors like citalopram, fluoxetin paroxetine and alaproclate downregulate Beta receptors. Trial with selective NE uptake blockers like maprotoline, nomifensine (inhibits DA uptake also) and mianserin , the a_2 antagonist, may throw clues on mechanism of anxiety disorder.

Beta blockers

Propranolol relieves somatic signs and symptoms of anxiety and can

block isoproterenol induced anxiety like symptoms (Carlesson et al. 1976, Keiholz 1977). Short term propranolol does not prevent lactate induced panic disorders (Gorman et al. 1983). The therapeutic effects of Beta blockers may also be partially linked to the effect on the peripheral organs. If high doses of propranolol are stopped suddenly panic symptoms may occur. These groups of drugs effectively increase airway resistance but drugs that do not possess significant Beta 2 activity may be of value in treatment of anxiety. Beta-l (or Cardio selective) blockers are metoprolol, atenolol and aceto butolol. In large dosage they inhibit all Beta receptors (Prichard 1978). Therefore, the conclusion on the role of Beta-l receptors in mediating anxiety reaction may be viewed as preliminary.

Conclusion

There seems to be a fundamental pathophysiologic difference between panic disorder and generalised anxiety. The generalised anxiety disorders in most are ameliorated by benzodiazepines, whereas the panic disorder are best treated by TCA and MAOI. The antidepressant "term" can mislead clinician that anxious persons with panic disorders are not depressed hence do not require antidepressants. The new benzodiazepine alprazolam that is effective in panic disorder has also differential effect on NE system through benzodiazepine receptors. The age old speculation that lactate is responsible for neuroaesthenia can be used to induce panic attacks. Yohimbine has been successfully used as a challenging agent. The future developments in molecular pharmacology may help in resolving the confusing issues related to these two syndromes and hence the therapeutics.

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