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Pharmacological Optimization of Military Performance: Anti-Anxiety Agents

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The possibility of a "brave pill" was considered for potential field utility by the Psychopharmacology Study Group, Division of Neuropsychiatry, WRAIR. Such a compound might markedly enhance combat effectiveness through its direct psychomotor effects and indirectly through the prevention and treatment of psychological battle casualties. In addition to troop preparedness and effectiveness achieved through rigorous, realistic field training, use of these agents on the battle field may provide a decided tactical advantage. Although no such compound exists in pure form, drugs of several classes produce prominent behavioral effects which may be reasonable to consider at the present time.

The development of anxiety, chronic and disabling or acute and overwhelming, has generally been the most significant symptom related to combat breakdown during wars of the 20th century (Bar-On et al., 1983). Moreover, anxiety may significantly reduce combat efficacy in the remaining combat force (cf. Roberts, 1983). The nature of future battlefields is expected to rapidly produce anxiety and psychiatric casualties in excess of optimal levels. Moreover, the fluid, high-intensity, continuous warfare previously encountered (eg., 1973 Arab-Israeli War and 1982 War in Lebanon) revealed that the current doctrine of forward treatment (Glass, 1973) may be increasingly difficult to apply in future conflicts (Belenky et al., 1983). Such conditions of warfare not only underscore the need to maximize preventive measures but also call for novel approaches which include unit treatment of casualties during battle and even the use of prophylactic drugs. The prevention of excessive anxiety or its effective treatment after its appearance will have an important impact on combat strength and will undoubtedly be essential to success in future conflicts (Ingraham and Manning, 1980).

Fear and anxiety are related psychological phenomenon that share many common attributes with symptoms of apprehension and reduced ability to concentrate, perform, or make decisions. The causes of anxiety and fear are various but it is generally agreed that physiological and psychological stress, abundant in combat, is a principle instigator and maintainer of these states and an associated battle-shock syndrome (Belenky et al., 1983).

Our knowledge of the pharmacological basis of anxiety and fear has advanced tremendously in the past few years. Clinically-effective compounds (anxiolytics, anti-anxiety drugs, or minor tranquilizers) are presently available which may be of great field utility as prophylactics against anxiety and/or required tools for the treatment of these disorders once they arise. Benzodiazepines, so named for their chemical structure, are the most widely used anxiolytics today. Relative to previous generations of anti-anxiety agents, few deleterious side-effects or other pharmacological properties complicate the use of benzodiazepines.

Benzodiazepines produce four major effects: anxiolytic, anticonvulsant, muscle relaxant, and sedative. In addition to direct anxiolytic activity benzodiazepines may provide additional protection against stress; eg. these drugs have been reported to markedly reduce stress-induced ulcer formation. Benzodiazepines as a class vary widely in terms of their durations of action and the production of active metabolites. Although a host of benzodiazepine compounds have been described, no significant improvement in

activity over diazepam (Valium) or chlordiazepoxide (Librium) has been noted except for increases in the diversity of durations of action.

Earlier non-benzodiazepines, ethanol, barbiturates, and propanediols such as meprobamate and other more recent compounds such as methaqualone suffer from their lack of specificity of anxiolytic effect more so than do the benzodiazepines. In addition, these classic non-benzodiazepine sedative-hypnotic anxiolytic agents produce profound physical dependence (sometimes life-threatening) and psychological dependence as reflected in their abuse liability. Benzodiazepines suffer from these problems only to a limited extent.

Newly-developed non-benzodiazepine compounds show unique promise as anxiolytics. Zopiclone may be less sedating than benzodiazepines and tracazolate clearly shows a greater separation between anxiolytic and sedating doses. PK 8165 and PK 9080 are similar to tracazolate in this respect as are the triazolopyridazines (eg. CL 218,872) but these four compounds have yet to prove themselves in the clinic and to reliably show anxiolytic activity across a host of preclinical tests. All of these non-benzodiazepines appear to work through mechanisms much akin to those of the benzodiazepines (see below). The novel antipsychotic, clozapine, a dibenzodiazepine, also shows evidence of anti-anxiety potential.

Buspirone is perhaps the best available non-benzodiazepine for treatment of anxiety. It is non-sedating, has minimal effects on human psychomotor performance, does not seem to produce physical dependence and is unlikely to be a drug of abuse. In addition, buspirone counteracts catalepsy (immobility). Moreover, unlike other anxiolytics, buspirone does not interact with other central nervous system depressants such as ethanol to further impair performance. Buspirone is well advanced in clinical trials and may well take over much of the anxiolytic drug market. Although the mechanism of action of buspirone is unknown, it is clearly very different than that of the anxiolytics currently available. Elucidation of the mechanisms responsible for buspirone's effects will provide an important new development in our understanding of the neurobiology of anxiety and its control.

A behavioral effect shared by all anxiolytic drugs is the disinhibition of suppressed or punished behavior. The ability of anxiolytics to increase the occurrence of behavior suppressed by response-produced consequences may be the primary behavioral mechanism of anxiolysis. This pharmacological action serves as the basis for preclinical anti-anxiety drug screening. Performance enhancements are also noted with anxiolytics in situations in which behavior has been suppressed by a novel or stressful environment. Benzodiazepines not only increase already suppressed behavior but also protect against the suppressive effects of noxious stimulation (Witkin, unpublished observations).

Receptors in brain have recently been determined to be the primary structures which, by virtue of their specific binding of drug molecules, initiate the neural events associated with the anti-anxiety activity of benzodiazepines. Benzodiazepine receptors appear also to be involved in the mechanism of action of some non-benzodiazepine compounds such as the barbiturates. Multiple benzodiazepine receptor subtypes have been identified and this discovery may lead to the development of drugs which more precisely control anxiety. The existence of benzodiazepine receptors in brain suggest the involvement of a substance(s) inherent in brain which normally regulate neuronal substrates of anxiety. Several such endogenous ligands have been identified but no substance thus far has been definitively identified as the physiological regulator of anxiety. However, future studies in this area may eventuate in the establishment of novel and perhaps more beneficial means of controlling anxiety.

The binding of compounds to the benzodiazepine receptor initiates a complex series of neurochemical events. Two important systems have been studied more so than others: gamma-aminobutyric acid (GABA) and serotonin neurotransmission. Both of these systems appear to play important roles in the anxiolytic actions of benzodiazepines and other drugs; compounds which block serotonin receptors may also be useful anxiolytic

agents. The precise manner in which neurotransmission is affected by anti-anxiety agents is unknown.

Compounds have been developed in the past few years which can reverse (antagonize) or prevent all known effects of the benzodiazepines. Ro 15-1788 (flumazepil) is one such compound. Unlike Ro 15-1788, which selectively antagonizes effects of benzodiazepines and other compounds which directly bind to benzodiazepine receptors, CGS-8216 antagonizes pharmacological actions of some non-benzodiazepines as well (eg. barbiturates, meprobamate). Ro 15-1788 has little intrinsic activity but when given in relatively high doses it has some benzodiazepine-like actions. Another class of compounds, 3-substituted beta-carbolines, sometimes referred to as inverse agonists, may produce their benzodiazepine antagonist activity by producing pharmacological actions which are opposite to those of the benzodiazepines; these compounds can themselves induce wakefulness, anxiety, and seizure activity which is reversed by Ro 15-1788 or diazepam. Antagonists may soon be developed which will reverse all but select actions of antianxiety drugs. It must be recognized that the development of such antagonists raises the possibility of their use as offensive weapons. Such drugs might have important advantages over other incapacitating or lethal agents, particularly when used clandestinely.

Antagonists may allow for further refinement of the pharmacological effects of anxiolytic drugs. For example, in a combat setting, an anxious, hyperactive, possibly aggressive patient could be given a hypnotic dose of a benzodiazepine. In the later event of a requirement to move the patient to a forward treatment facility, the soldier could be given an antagonist to reverse all but the anti-anxiety actions of the benzodiazepine. For a soldier experiencing severe anxiety in a forward area, an anti-anxiety drug might be given by the medical aidman or even the squad leader. The soldier could then avoid all of the problems of rearward evacuation.

Another class of drugs that appears to posses anxiolytic activity is the beta-adrenergic antagonists such as propranolol and the alpha-adrenergic antagonists such as clonidine. Such agents could serve as a prophylactic treatment in soldiers exposed to battle conditions producing chronic autonomic arousal (Jones, 1983b). These agents seem to have little potential for dependence or abuse, and may be particularly effective when somatic elements of anxiety are prominent. Thus these compounds can improve weapon marksmanship by reducing normal muscle tremor which is accentuated by anxiety or fear. Normal components of the diet, amino-acids and neurotransmitter precursors, may produce psychological alerting effects as well as sedative or anxiolytic actions deserving of further examination (cf. Hegge and Tyner, 1983; Jones, 1983a).

The problems of drug tolerance, dependence, and withdrawal have severely limited the usefulness of sedative, tranquilizing agents in the past. Tolerance refers to the reduction in the effects of a drug that accompany repeated administration such that higher doses, with greater risks of side-effects, are required to reproduce initial drug effects. Tolerance, principally pharmacodynamic in nature, develops to many of the effects of the benzodiazepines such as sedation and muscle relaxation; anxiolytic activity of benzodiazepines, however, does not diminish with repeated dosing but may increase. In fact, a "drug-naive" effect has been reported in which initial treatment does not result in anti-anxiety effects. Thus some of undesirable effects of the benzodiazepines such as decrements in motor and cognitive function may be mitigated by repeated administration.

Drug dependence and withdrawal may present more serious problems in combat. Two types of dependence may develop upon repeated drug administration. Psychological dependence refers to the establishment of a drug as a positive reinforcer; dependence of this sort is associated with the maintenance of behavior by the acquisition and self-administration of the drug and is typically accompanied by feelings of drug craving. Physical dependence is defined by the production of physiological and behavioral changes (withdrawal signs) which occur upon the abrupt termination of chronic drug

intake or upon administration of an antagonist. Although physical dependence need not be present for psychological dependence to develop, these two types of dependence severely compromise and complicate the use of sedative-hypnotic/anxiolytic drugs in the field. Physical dependence with rebound anxiety, autonomic arousal, and insomnia have been documented for the benzodiazepines as well as for earlier generation sedative-hypnotic/anxiolytics such as the barbiturates which produce additional withdrawal symptoms (eg. convulsions, hallucinations, death). Shorter acting benzodiazepines appear to have greater physical dependence liability than longer acting ones. Of the antianxiety agents currently in use, the benzodiazepines are least abused, and least likely to produce dependence problems. Newer anxiolytics (eg. buspirone) may be completely free of these problems.

Concurrent use of antianxiety agents with other compounds may result in unwanted effects and may in some cases produce life-threatening consequences. Currently used antianxiety agents suffer from their prominent interactions with other central nervous system depressant drugs including other sedative compounds and ethanol resulting in sedation, hypnosis, and ultimately respiratory arrest. Newer anxiolytics appear to be relatively immune to this synergistic action. In other cases, combinations of anxiolytics with other drugs produce some desirable outcomes. When given in conjunction with appropriate doses of d-amphetamine, benzodiazepines and barbiturates may produce greater anxiety reduction than either drug alone as well as a qualitatively unique pharmacological profile. Although such drug combinations may be quite prone to drug abuse, their unique behavioral and subjective effects may render them more efficacious than anxiolytics alone as brave pills (eg., feelings of invulnerability). Drug combinations may also allow use of lower levels of the anxiolytic drug without compromising the clinical or field objective. For example, thyrotropin-releasing hormone potentiates the antianxiety actions of benzodiazepines, barbiturates and ethanol, without having actions of its own; thus the dosage levels of the sedative/anxiolytic agents can be reduced, lessening chances for deleterious side-effects (Witkin et al., 1984). Other clinically-important or militarily-relevant adverse benzodiazepine-drug interactions are rare.

All drugs produce unwanted effects although some compounds do so to a greater extent than others. These so-called side-effects, discussed above, must be considered. For example, animal studies have indicated that anxiolytics may decrease aggression. The consequences of possible disruptions in normal combat-stress reactions resulting from the use of drugs is not well defined. Drugs do not produce unitary effects on behavior; behavioral effects of drugs depend upon a host of subtle controlling variables such as environmental context, motivation, and behavioral and pharmacological history (Barrett and Witkin, 1985; McKearney and Barrett, 1976). Interaction of drugs and behavior on the battlefield can not be precisely predicted. Soldier compliance with a prophylactic drug doctrine may also be a problem. Some soldiers may benefit more than others from such treatment whereas some personnel may be treatment risks (eg. potential drug abusers). Means of identification of these subpopulations are desirable.

Drugs are currently available which relieve anxiety yet produce few deleterious side-effects. The benzodiazepines and buspirone look most promising in this regard. The development and refinement of novel drugs for controlling fear and anxiety will likely be forthcoming. The availability of antagonists to the anxiolytic agents provides a rapid means of controlling drug action; eg. reversal of drug overdose or idiosyncratic effects. Non-drug techniques for controlling fear and anxiety (particularly diet, behavioral conditioning and stress- inoculation) may also be useful alone or in combination with anxiolytic agents. Rigorous laboratory and field studies are urgently required to evaluate the utility of these ideas. The technical skills, physical conditioning, confidence, unit cohesion and esprit, natural by-products of good training and leadership, are key components of an effective fighting force. None of the drugs discussed above can substitute for appropriate military training and leadership but may provide decided

combat advantages with appropriate field use.

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