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MEETING REPORT

New concepts in anxiety

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An international symposium on New Concepts in Anxiety, organised by Mike Briley (Centre de Recherche Pierre Fabre, Castres, France) and Sandra File (Psychopharmacology Research Unit, Guy's Hospital, London, UK), was held in Castres (France) 4–6 April 1990. The meeting, sponsored by the Pierre Fabre Research Centre with contributions from ITEM-LABO and Elevage Janvier, attracted 200 participants from 20 countries.

The speakers covered the subject from molecular biology to clinical trials and from 5-HT receptor subtypes to experimental psychology of cognition in anxiety. Most of the speakers took the theme "New Concepts" very seriously and a number of original ideas of various aspects of anxiety were presented.

The high scientific standard, was set by the first speaker, G. Gray (Institute of Psychiatry, London, UK), who showed how septal stimulation could increase or decrease hippocampal theta rhythms of rats depending upon the animals' sensitivity (and previous exposure) to anxiogenic stimuli, suggesting that drugs acting on a more of less "anxious" substrate may not necessarily have the same effect. He then went on to describe experiments with two inbred strains of rats characterized for their high level of "anxious" behaviour (Maudsley Reactive and Roman Low Avoidance strains). mRNA extracted from these strains gave a number of in-vitro translation products which were not found in the "low anxiety" equivalents or in standard outbred strains. He suggested that these proteins may result from genes associated with high levels of anxiety.

Benzodiazepines are dead—long live benzodiazepines!

S. File showed that the problems of dependence and withdrawal following long-term benzodiazepine administration are real and can be readily demonstrated in animals. Three weeks administration of benzodiazepines is enough to produce anxious behaviour in rats upon withdrawal. Flumazenil, a benzodiazepine antagonist, can reverse this rebound anxiety in the same way as it can antagonize the anxiolytic effects of the benzodiazepines. D. Nutt, (Reckitt & Colman Psychopharmacology Unit, Bristol University, UK) suggested that the explanation for this bidirectional effect may lie in modifications that benzodiazepine receptors undergo during prolonged treatment. There may be a shift in the agonist:partial agonist:antagonist:partial inverse agonist:inverse agonist spectrum such that partial agonists may be recognised as full agonists and so on.

Mechanisms which might be exploited to find new drugs to treat anxiety without these side-effects were a recurrent theme. Several approaches to benzodiazepine-like drugs lacking the side-effects of the current drugs were discussed. P. Skolnick (NIH, Bethesda, USA) presented data showing that the benzodiazepine-GABA-chloride channel complex consists of at least six distinct types of α-subunit combined with a γ-protein so that the possible number of combinations may be enormous. In addition he suggested that the benzodiazepine binding site was probably not at the core of the complex but rather at the periphery and made up of a variety of protein chains from different subunits. This situation should provide rich possibilities for finding drugs with slightly different binding characteristics or possessing only a part of the classical benzodiazepine profile.

D. Nutt explained that partial agonists acting at the benzodiazepine receptor could theoretically provide another approach although it is too early to have any clinical feedback. The possible role of an endogenous ligand for the benzodiazepine receptor in anxiety was also evoked by D. Nutt but he felt that anxiety disorders probably lay more in a dysfunction of the benzodiazepine receptor itself and that there was no need to postulate an endogenous anxiogenic or anxiolytic ligand. Nevertheless the existence of a ligand remains a possibility and several groups are actively pursuing this approach encouraged by the report of low levels of benzodiazepines themselves in various plant and bacterial sources (Wildmann et al 1988).

On the basis of electrophysiological data, P. Polc (Hoffmann-La Roche, Basel, Switzerland) suggested that GABA-independent mechanisms may also play an important role in the action of benzodiazepines. These effects are possibly related to Ca^{2+} and/or K^+ conductance, adenosine uptake and/or CCK antagonism. Biochemically, benzodiazepines have been shown to decrease noradrenaline release by a GABA-independent mechanism and behaviourally there are a number of points that are difficult to reconcile with an exclusively GABA-related activity. The mechanism of the antianxiety activity of the benzodiazepines is therefore still not really answered.

5-HT—all things to all (anxious) men

As was to be expected 5-HT was very prominent in this meeting. The organisers had reserved nearly a whole day for the subject. In addition many speakers in other areas touched on the subject as did a number of the 30 poster presentations. M. Briley introduced the subject with a review of the effects of a variety of compounds active on 5-HT neurotransmission in different animal models. From these studies he concluded that stimulation of 5-HT neurotransmission tended to increase anxiety. He then went on to point out, however, that if 5-HT neurotranmission was studied in animals showing high or low levels of anxiety (experimentally induced or genetically determined e.g. Fawn Hooded rats) 5-HT neurotransmission was highest where anxiety was lowest and vice versa. This, he suggested, could be reconciled by hypothesizing that a certain "ideal" anxiety level is homeostatically controlled by a 5-HT-dependent system.

D. Grahame-Smith (Radcliffe Infirmary, Oxford, UK) started his talk by deploring the passing of those halcyon days when we all believed that the brain was like a plastic bag full of Ringer's solution in which receptors and neurotransmitters floated and interreacted and that a 5-HT receptor was simply a 5-HT receptor. He went on to show just how false that image has become and that the 5-HT system has various levels of heterogeneity. Structurally and functionally there are at least two types of systems and numerous interacting modulatory systems. This multi-faceted system can therefore offer innumerable ways of controlling anxiety. This means that the effects and the side-effects of drugs acting on different sites will probably be

different. For this reason and since prediction from animal models is precarious, careful study of human anxiety with each type of drug is fully justified.

Drugs that act at 5-HT_{1A} receptors as agonists or partial agonists appear to belong to a new generation of anxiolytics. J. Traber (Troponwerke, Cologne, West Germany) stressed the importance of the septohippocampal system which is innervated by the raphe. He explained that the pyrimidinylpiperazines (buspirone, gepirone and ipsapirone) are all partial agonists at postsynaptic 5-HT_{1A} receptors in the hippocampus, having different intrinsic activity in inhibiting the 5-HT_{1A}-linked adenylate cyclase. At the presynaptic 5-HT_{1A} receptor in the raphe, however, they are all full agonists as measured by inhibition of raphe firing. This unique property, he believes, is at the origin of their now well demonstrated anxiolytic activities.

1-(3-Chloro)phenylpiperazine (mCPP) is a metabolite of the antidepressant drug, trazodone. When given directly to man it has been shown to exacerbate anxiety, panic disorders and other associated conditions. G. Curzon (Institute of Neurology, London, UK) showed that similar effects could be obtained in animals with both mCPP and the closely related 1-(3-trifluoromethyl)phenylpiperazine (TFMPP). Using an impressive array of detailed behavioural experiments he demonstrated that this anxiogenic activity probably results from stimulation of the hippocampal 5-HT_{1C} receptors. He suggested that 5-HT_{1C} antagonists may provide an interesting new approach to anxiolytic therapy.

J. F. W. Deakin (Manchester University, UK) took a clinical pharmacological approach to study the role of 5-HT_2 receptors in anxiety. He chose the 5-HT_2 antagonist, ritanserin, to test his hypothesis that the slow onset of action of the 5-HT_{1A} partial agonists, such as buspirone, was the result of 5-HT_2 receptor down-regulation. If this were true 5-HT_2 antagonists should be directly anxiolytic. In normal volunteers, ritanserin decreased the retention of aversive conditioning which could be related to anxiety. In a population of mixed anxiodepressives, however, the anxiolytic effects of ritanserin were not convincing.

D. Piper's (Beecham Pharmaceuticals, Harlow, UK) balanced and prudent review of the evidence for the potential anxiolytic activity of 5-HT_3 antagonists was particularly welcome in view of the overstatement often associated with this class of compounds. He felt that in spite of some conflicting data the weight of the evidence was in favour of these drugs representing a new class of anxiolytics. Although D. Piper declined to comment on the ongoing clinical studies with these compounds, a poster from J. Pecknold, L. Luthe, L. Iny and M. Meany (Douglas Hospital, Montreal, Canada) showed some preliminary but encouraging anxiolytic findings with zacopride.

A major difficulty in developing serotonergic compounds in anxiety has been to find animal models in which they respond. In general, they failed to show anticonflict activity in rodents, an activity classically related to the anxiolytic activity of benzodiazepines. Moreover these new compounds show non-linear dose-effect relationships with often only a very narrow active dose range. Mechanisms suggested to explain this include differences in 5-HT receptor function depending on the level of anxiety of the animal (M. Briley). The difficulties in adapting tests to the new non-benzodiazepine anxiolytics is not, however, limited to animals. M. Ansseau (CHU Sart Tilman, Liège, Belgium) showed that a new approach to the early clinical testing of non-benzodiazepine (and even atypical benzodiazepine) anxiolytics was needed. He outlined to what extent the formula "anxiolytic = benzodiazepine" is anchored in the subconcious of patients as well as clinicians. It is clear that if the newer anxiolytics are to replace, at least partially, the benzodiazepines, a major educational programme for patients, doctors and registration authorities will be needed.

. . . and all the other neurotransmitter systems

Anxiety does not involve only benzodiazepine receptors and 5-HT neurotransmission; full recognition was given to other neurotransmitter systems which are, or could be, involved in anxiety. The role of noradrenaline was reviewed by A. Johnston (Medical University of South Carolina, Charleston, USA) who concluded that increased noradrenergic transmission, especially locus coeruleus firing, may be associated with certain types of anxiety and particularly panic disorders.

An integrative approach was taken by F. Graeff (University of São Paulo, Brazil) who presented the effects of various drugs on the behaviour elicited by electrical stimulation of the dorsal periaqueductal grey region, which appears to be a key region in the development of panic attacks.

The role of excitatory amino acids in the control of anxiety was the subject of two presentations. D. Stephens (Schering AG, Berlin, West German) explained that glutamate and aspartate act at excitatory synapses in a similar but opposite way to GABA. Thus, if stimulation of GABA neurotransmission (by benzodiazepines for example) decreases anxiety, a reduction of glutamatergic transmission should lead to similar results. Antagonists of the NMDA subtype of glutamate receptor elicit similar effects of benzodiazepines in several animal tests predictive of anxiolytic activity. However, the possible anxiolytic properties of such compounds has not yet reached the level of clinical testing. The activity of antagonists at other glutamate receptor subtypes is still an open question since the compounds currently available have very poor brain penetration.

P. Skolnick presented data showing that antagonists of the strychnine-insensitive glycine receptor, such as 7-chlorokynurenic acid, or the partial agonist, 1-aminocyclopropanecarboxylic acid (ACPC), also had anxiolytic-like activity in animal tests. He felt that this activity may be mediated indirectly through the NMDA receptor complex where glycine has an important modulatory role.

Without forgetting cognitive aspects of anxiety

The problems of cognition in relation to anxiety and benzodiazepine use was the subject of a whole session. A number of studies with normal volunteer subjects demonstrated clearly that benzodiazepines do impair memory but whether such effects are specifically "amnesic" or simply a by-product of reduced vigilance is debatable (H. V. Curran, Institute of Psychiatry, London, UK). On the other hand, aspects of attentional functioning, which might be summarized as hypervigilance, appear to form part of a cognitive vulnerability in generalized anxiety disorder (M. Eysenck, University of London, UK; R. Lister, NIAAA, Bethesda, USA). From this viewpoint any successful anxiolytic treatment will inevitably tend to decrease cognitive performance to some extent.

The development of specific benzodiazepine inverse agonists and inverse partial agonists such as various β-carboline derivatives has permitted the testing of the hypothesis of the bidirectional activity of benzodiazepine receptors. The development of inverse partial agonists for improving cognitive functioning (T. Duka, Schering AG, Berlin, West Germany) is an interesting spin-off from anxiety research which is giving encouraging preliminary results.

Panic disorders

Generalized anxiety disorder and panic disorder do not meet the same criteria and do not respond to the same therapy, suggesting that different mechanisms are involved. The role of noradrenaline in panic disorder was discussed by J. C. Bisserbe (CHU Côte

de Nacre, Caen, France) while J. Bradwejn (McGill University, Montreal, Canada) showed an interesting video film of a panic attack induced by cholecystokinin (CCK).

In conclusion

In his summing up, D. Nutt pointed out that receptor selectivity, especially 5-HT receptor selectivity, is still a goal of most drug companies seeking to develop new anxiolytic drugs. He contrasted this with some other areas of neuropharmacology where there is a tendency to return to "dirty drugs". The screening of these new compounds in animal tests is difficult due to their lack of classical dose-effect relationships. It is becoming obvious that the basal levels of anxiety can determine to a large extent not only the degrees but the direction of the response of potential drugs both in animals and in clinical testing.

Finally it seems clear that anxiety must be considered not only as a symptom present in a wide variety of syndromes but in many circumstances as a beneficial (increased vigilance) or detrimental (morbid anxiety) adaptive phenomenon. Significant progress in the therapy of anxiety can only come from a better understanding of the fundamental mechanisms implicated in the origin, development and regulation of anxiety in animals and in man.

The full proceedings of this meeting will be published by Macmillan Press as Volume 4 of the Pierre Fabre monograph Series under the title "New Concepts in Anxiety" by M. Briley and S. File.

References

Wildmann, J., Vetter, W., Ranalder, U. B., Schmidt, K., Maurer, R., Möhler, H. (1988) Occurrence of pharmacologically active benzodiazepines in trace amounts in wheat and potato. Biochem. Pharmacol. 37: 3549–3559