Pharmacology Biochemistry & Behavior, Vol. 29, pp. 767–769. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Behavioural and Neural-System Analyses of the Actions of Anxiolytic Drugs

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GRAY, J. A. *Behavioural and neural-system analyses of the actions of anxiolytic drugs.* PHARMACOL BIOCHEM BEHAV **29**(4) 767–769, 1988.—Anti-anxiety drugs (including benzodiazepines, barbiturates and alcohol) have a distinctive profile of behavioural action in animal species ranging from goldfish to chimpanzee. This profile may be summarised as a blockade of three kinds of reaction (behavioural inhibition, preparation for vigorous action, and increased attention to the environment) in response to any of three kinds of stimuli (novelty, stimuli associated with punishment, or stimuli associated with frustrative nonreward). On this basis, one may postulate a 'behavioural inhibition system' in the brain, responsible for organising the above reactions in response to appropriate stimuli; activity in this system would then constitute 'anxiety.' One may attempt to describe the brain structures that constitute the behavioural inhibition system either by enquiring about the neurochemical mode of action that is common to anti-anxiety drugs, or by seeking for structures with appropriate behavioural functions. The latter approach has implicated a number of structures in the limbic system (including the hippocampal formation, the septal area, and ascending monoaminergic pathways). Possible information-processing functions of these structures are described.

Anxiolytics Behaviour Anxiety

IN the development of novel, non-benzodiazepine anxiolytics it will be of value to bear in mind what is known about existing anxiolytics in respect of the following questions: (1) What behaviour do they alter? (2) By what neurochemical steps do they act? (3) Via which brain systems do they act? (4) What cognitive processes do they affect? (5) How do they alter the clinical symptoms of anxiety? I shall briefly consider likely answers to these questions.

A comprehensive answer to question (1) is presented in Fig. 1. This states that anxiolytics block three kinds of behavioural response (inhibition of ongoing behaviour, increased attention to the environment, and increased readiness for rapid and vigorous action, that is, an increment in 'arousal') to three kinds of stimuli (stimuli associated with punishment, stimuli associated with non-reward, and novel stimuli). Note that this generalisation is based on a large number of experiments [1] that used two previous classes of non-benzodiazepine anxiolytics (ethanol and barbiturates) as well as benzodiazepines, and that little qualification with respect to the particular class of anxiolytics is required. Thus there is every reason to suppose that Fig. 1 will apply also to novel non-benzodiazepine anxiolytics.

The answer to the second question—by what neurochemistry?—appears to be well-known: benzodiazepines facilitate the action of GABA at $GABA_A$ receptors after binding to the specific benzodiazepine receptor that is closely associated to these GABA receptors (Langer, this meeting); and barbiturates and ethanol also facilitate GABAergic inhibition, though by different detailed mechanisms. However, it is still not established that this neurochemical action is the basis of the specifically anxiolytic action of existing anxiolytics. Evidence from my own laboratory supports this hypothesis (with some exceptions) for the benzodiazepines, but not for the barbiturates [4].

Furthermore, even if anxiolytics reduce anxiety in virtue of their effects on GABAergic transmission, this alone does not account for the behavioural selectivity of the anxiolytics (Fig. 1), nor do any existing biochemical theories (in terms of receptor heterogeneity, etc) manage to produce such an account. One possibility is that anxiolytics increase GABAergic inhibition in whatever circuits are activated in a given situation. The selectivity for the reduction of anxiety would, on this account, lie in the anxiogenic situation, not principally in the neurochemistry of the drug [3].

A further way to approach the question of selectivity is to address question (3) above: via what brain systems do the anxiolytics act? An answer to this question was given by Gray [2]. According to this theory, the major mode of action of existing anxiolytics is to reverse the stress-induced increase in the activity of ascending noradrenergic and serotonergic fibres which, in the undrugged animal, enhances the information-processing capacity of the septohippocampal system and its allied Papez circuit and puts this capacity at the service of the analysis of threat (see Fig. 2). This action of the anxiolytics is likely to be mediated via the GABAergic receptors located both on the relevant cell-bodies (in the locus coeruleus and median raphe nuclei) and at their terminals in the forebrain. The brain system depicted in Fig. 2 as being important for the state of anxiety was deduced in the first instance from studies of the behavioural effects of anxiolytic drugs. However, it has received support from a number of other, diverse directions, including psychogenetic studies with rats and mice; investigations of the effects of early environmental manipulations that perma-

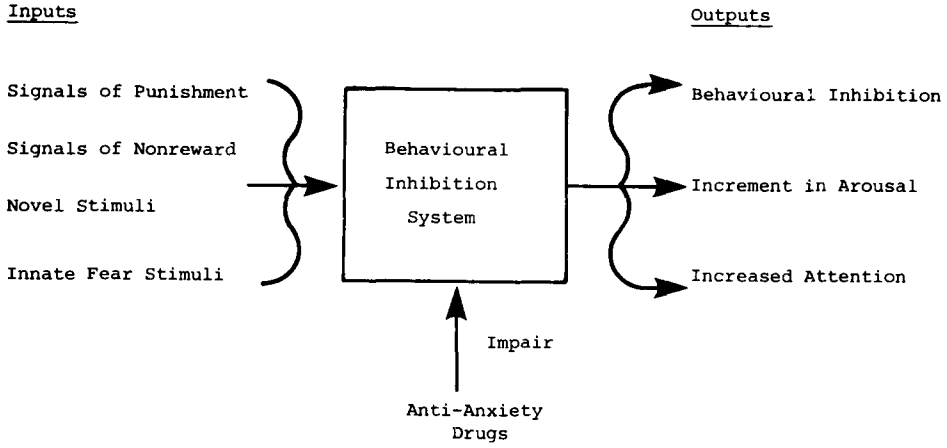

FIG. 1. The behavioural inhibition system.

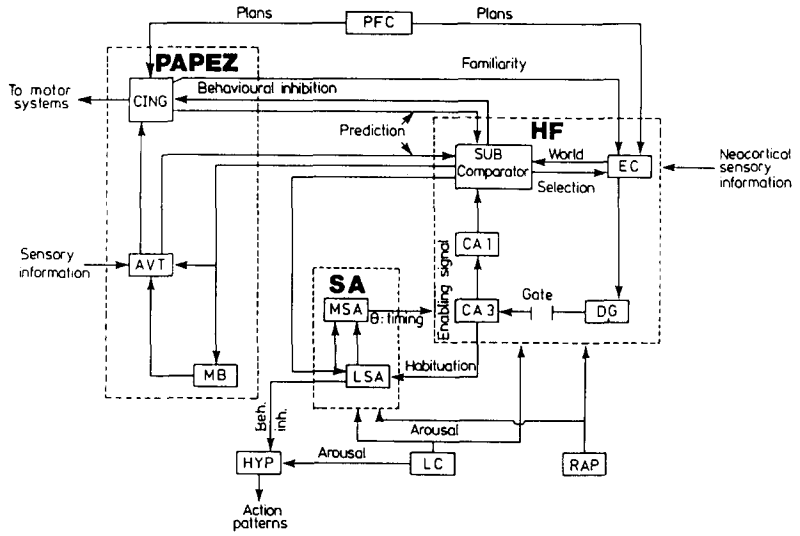

FIG. 2. A summary of the theory developed by Gray [2]. The three major building blocks are shown in heavy print: HF, the hippocampal formation, made up of the entorhinal cortex, EC, the dentate gyrus, DG, CA 3, CA 1, and the subicular area, SUB; SA, the septal area, containing the medial and lateral septal areas, MSA and LSA; and the Papez circuit, which receives projections from and returns them to the subicular area via the mammillary bodies, MB, anteroventral thalamus, AVT, and cingulate cortex, CING. Other structures shown are the hypothalamus, HYP, the locus coeruleus, LC, the raphe nuclei, RAP, and the prefrontal cortex, PFC. Arrows show direction of projection; the projection from SUB to MSA lacks anatomical confirmation. Words in lower case show postulated functions; beh. inh., behavioural inhibition.

nently alter anxiety level in the rat; positron-emission tomography of patients who suffer from panic attacks; and studies of the biochemical and behavioural reactions of such patients to drugs that increase the activity of central noradrenergic neurons.

The chief function of the brain is to process information. Thus, given a system of the kind illustrated in Fig. 2, it is reasonable to proceed to our next question, namely, what information-processing functions does this system discharge? This is tantamount to asking, what cognitive processes are altered by anxiolytic drugs? In answer to this question, Gray [2] has proposed that the septohippocampal system, together with the other structures illustrated in Fig. 2, has the general function of acting as a comparator (Fig. 3), that is, predicting the expected state of the animal's world in the next instant of time (approximately 0.1 sec), and comparing this prediction to the actual state of the world as fed into the septohippocampal system from neocortical sensory analysing systems via the entorhinal cortex. In making the relevant predictions the system draws upon descriptions of

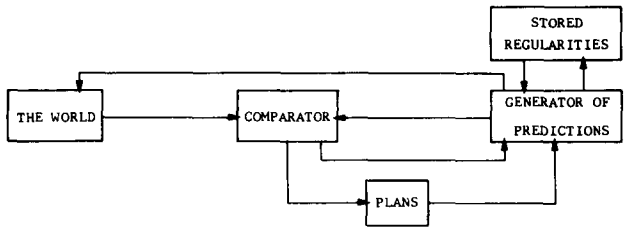

FIG. 3. The kinds of information processing required for the successful functioning of the hypothetical comparator [2].

previous regularities (of stimulus-stimulus and response-stimulus kinds, derived respectively from Pavlovian and instrumental conditioning) stored in the temporal lobe, and upon a description of the animal's current motor program, sent from the prefrontal cortex to the entorhinal and cingulate cortices (Fig. 2). If the actual event is successfully matched to the predicted event, the system continues in 'checking mode' to make the next prediction and compare it to the next sample from the world, control over behaviour resting with other brain systems. If however, the actual event does not match the predicted one, or if the predicted event is aversive (i.e., punishment or non-reward), then the system enters 'control mode,' takes control over behaviour and operates the outputs of the behavioural inhibition system (Fig. 1).

We may now turn to the final question addressed in this paper: how do the existing anxiolytic drugs affect the clinical symptoms of anxiety? The answer provided to this question by the theory outlined above is as follows. The information-processing activities (Fig. 3) discharged by the septohippocampal system (Fig. 2) are put to the service of the state of anxiety by way of an increase in ascending monoaminergic activity induced by threat (Fig. 1). In checking mode, these activities give rise to the type of cognitive symptom seen most clearly in the obsessive-compulsive syndrome (excessive checking for potential threat); in control mode, they give rise to the behavioural symptoms known as phobias. In addition, the descending influence of the noradrenergic fibres originating in the locus coeruleus are responsible for the autonomic symptoms of anxiety [5]. These symptoms would all therefore be expected to respond to anxiolytic medication (because of the reduction in stress-induced monoaminergic activity produced by the relevant drugs). In addition however, the information-processing activities of the septohippocampal system can come under the control of descending neocortical projections from the prefrontal cortex (Fig. 2), giving rise to some anxiety symptoms (especially prominent in obsessive-compulsive neurosis and prolonged neurotic depression) that do not respond to such drugs; while some autonomic symptoms of anxiety (especially prominent in panic attacks) appear to be due to activity in neurons of the central gray of the midbrain, and also fail to respond to these drugs.

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