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CHEMICAL STRUCTURE AND BIOLOGICAL ACTIVITY OF THE DIAZEPINES

P. DANNEBERG[1] & K.H. WEBER[2]

Departments of Pharmacology[1] and Medicinal Chemistry[2], Boehringer Ingelheim KG, 6507 Ingelheim am Rhein, Federal Republic of Germany

1 Since the introduction of chlordiazepoxide and diazepam many diazepines have been developed. Use of these drugs is increasing and considerable knowledge has accumulated about their mechanisms of action.

2 The structural and pharmacological properties of these drugs are surveyed briefly.

Keywords diazepines biological activity chemical structure

Structural features of the diazepines

The chemical structure of the benzodiazepines seems at first sight to be unique among the various types of central depressant drugs. However, a closer look reveals structural features which many central depressants have in common. For example, such drugs possess a carboxamide group as a constituent part of a five-, six- or seven-membered heterocyclic ring structure (Figure 1). The significance of this common feature has not yet been determined.

The many attempts to establish the connections between the chemical structures of central depressants and their pharmacological activities have so far met with only limited success. Correlations between physicochemical parameters and biological activities can be based only on small series of derivatives of one type of basic molecule. Thus, for example, it is not possible to optimize the structure of diazepines by using physicochemical correlations obtained from structure-activity studies in barbitu-

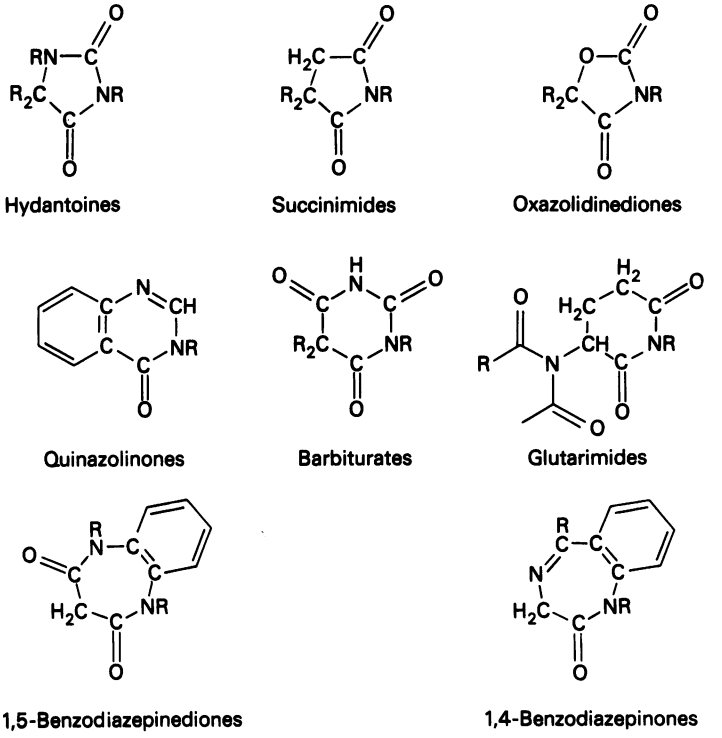


Figure 1 Structural similarities between central depressant drugs (anticonvulsants, tranquillizers, hypnogenics).

rate series. We will, therefore, have to consider the diazepine structure as an entity of its own when we attempt to ally its chemical features with its biological properties.

The diazepines (Figure 2) used today as anxiolytics, hypnotics or anticonvulsants are almost exclusively 1,4-benzo-diazepines (e.g. diazepam). The 1,5-diazepines have similar properties but considerably less sedative and hypnogenic activity (e.g. clobazam). Both structures require a substituent in the 7-position to exhibit activity and a halogen or a nitro-group have proved optimal in this respect. The activity of a diazepine molecule can also be increased by the introduction of a halogen in the ortho-position of the 5-phenyl ring (e.g. lorazepam).

During recent years, efforts have been made to replace the two phenyl rings by other ring structures. The substitution by pyridyl of the phenyl group in the 5-position resulted in bromazepam, which in man not only alleviates anxiety but also seems to exert psychomotor stimulating properties. Also the annelated phenyl-ring in the 6,7-position of the diazepine system can be replaced by heterocyclic systems, for example, a thieno- (e.g. clotiazepam) or a pyrazolo-ring (e.g. ripazepam).

Another possibility for modifying the benzodiazepine structure is the annelation of an additional ring system. The 1,2-annelation of triazole or imidazole resulted in highly active substances (e.g. triazolam and midazolam). In

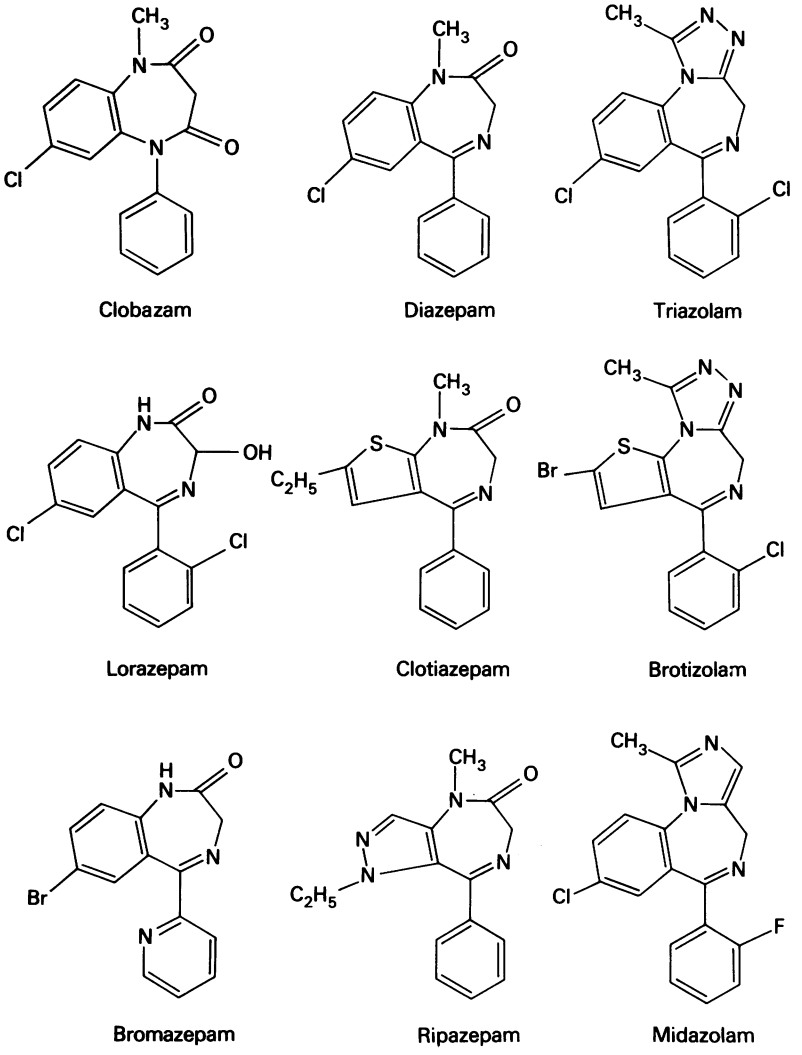


Figure 2 Examples of various diazepine structures.

Figure 2 the benzodiazepine (diazepam) and thienodiazepine (clotiazepam) structures are shown opposite their respective triazolo-congeners (triazolam and brotizolam). We have systematically investigated the possible variations of annelations in the 1,2- and 6,7-positions of the 1,4-diazepine structure and have shown that the combination of a triazolo-ring in the 1,2-position with a thieno-ring in the 6,7-position brings about optimal pharmacological activity. The triazolo-thieno-diazepine brotizolam, to our knowledge, is not surpassed by any other diazepine in respect of its affinity for benzodiazepine receptor sites.

The methyltriazolo-diazepines not only exhibit high pharmacological activity but are also metabolized differently from the 'classical' 1-*N*-methyl-diazepines (Figure 3). In both types of compound the methyl-group is hydroxylated; but only the 1-*N*-hydroxymethyl metabolite is easily hydrolysed resulting in a 1-*N*-desmethyl-diazepine which is pharmacologically active with a long half-life. In contrast, a hydroxymethyl-triazolodiazepine is stable to hydrolysation. Such hydroxy-compounds and their conjugates are excreted rapidly. Thus, when they are taken at bedtime to induce sleep, the effects last only during the night-time hours and a 'hang-over' effect will not occur the following morning, as by that time the compound and its metabolites have already been eliminated. Because of these properties, the methyltriazolo-diazepines may be expected to have particular advantages as hypnogenic drugs.

For most commercial diazepines, claims have been made to the effect that one of the various pharmacological qualities which all these drugs have in common is either absent or prevails in the drug under consideration. Clinical experience has indeed shown that this is possible. It has already been mentioned that the sedative properties of the diazepines, which for most members of the group are considerable, are only slight for clobazam, so that this drug seems to be particularly useful as a daytime anxiolytic. Another example is the occurrence of psychomotor stimulant properties reported for lorazepam and bromazepam, which make these drugs apparently useful in the treatment of retarded or inhibited behavioural states. However, as already pointed out, there is little knowledge about the relationships between individual pharmacological qualities of such diazepines and their particular chemical structures. So far, most of the structure-activity relationships which have been established refer to the general properties of the diazepines and not to particular components of their spectrum of activity.

The main pharmacological effects of the diazepines are exerted on emotional behaviour, muscular tone and motor coordination.

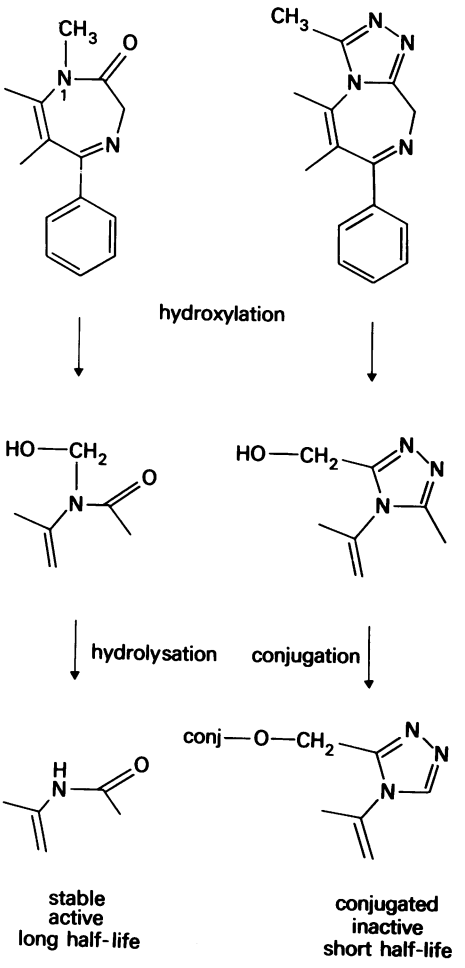


Figure 3 Differences in metabolism of the 1-*N*-methyl-diazepines and the methyl-triazolodiazepines. Both methyl groups are hydroxylated. The 1-*N*-methyl compound is easily hydrolyzed to the desmethyl-metabolite which is stable, pharmacologically active and has a long half-life, whereas the hydroxy-methyl-triazolo metabolite is rapidly excreted either unconjugated or in a conjugated form.

Behavioural effects

It is generally believed that the diazepines are central depressants, as they potentiate the effects of other central depressants and antagonize the effects of central stimulants. However, in contrast to the case with most central depressants, a reduction of spontaneous activity in experimental animals is difficult to demonstrate with diazepines, except when extremely high doses are used. In low doses the diazepines do not cause sedation, but rather an increase in behavioural activity. The relevant effects of diazepines on behaviour only come to

light in special experimental situations when hyper-emotional states are induced. The effects under such conditions may be interpreted as inhibitory or disinhibitory in nature, depending on the state of emotion and the situation studied. The reduction of arousability, the inhibition of aggression and the facilitation of sleep may be considered 'inhibitory' properties; the anti-anxiety and anti-frustration effects and also the induction of aggression may be interpreted as 'behavioural disinhibition' (Figure 4). Both these types of behavioural effect have been subject to intensive experimental research and are the two major therapeutic indications for the use of diazepines in man.

Anxiolysis

The anxiolytic properties of diazepines can be demonstrated in experimental situations in both animals and man. Usually a conflict is created between receiving an expected reward and receiving a presignalized simultaneous punishment which can only be avoided by dispensing with the reward (Geller & Seifter, 1960). Animals are considered to be 'anxious' when faced with such a conflict. Because of their fear of punishment they abstain from the activity required to obtain the reward. After being given a diazepine they recommence this activity in spite of the well-known warning signal preceding the punishment. As the animals apparently overcome their fear, this effect is interpreted as one of anxiolysis. As fear of punishment inhibits the undrugged animal in its drive to go for the reward, the underlying behavioural effect of diazepines may be considered disinhibitory.

Barbiturates, meprobamate and alcohol also have some effect in punishment-reward-conflict experiments, but in smaller dose ranges than the diazepines. Other types of psychopharmacological drugs, such as antidepressants and antipsychotics, are devoid of anxiolytic properties (Figure 5).

When, in a non-conflict situation, an expected reward repeatedly fails to appear, the drive of the conditioned individual to go for the reward is diminished. In this experimental situation, which is considered to reflect a state of frustration, the diazepines augment behavioural responses (Soubrié *et al.* 1978). Such an increase in the non-rewarded behaviour has been interpreted as an anti-frustration effect.

Behavioural mechanisms	*Behavioural effects*
Disinhibitory	Incitement of behavioural activity *anti-anxiety effects* *anti-frustration effects* *aggressive effects*
Inhibitory	Suppression of behavioural activity *reduction in arousability* *facilitation of sleep* *anti-aggressive effects*

Figure 4 The postulated two categories of behavioural mechanism of diazepines and the respective effects on various emotional states.

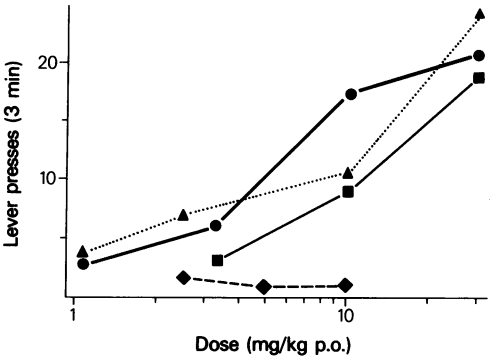


Figure 5 Disinhibitory action of diazepines (● brotizolam, ■ diazepam), a barbiturate (▲ phenobarbitone) and a neuroleptic (◆ chlorpromazine) in a punishment-reward conflict. Because of their fear of the punishment (electric-shock) the rats abstain from lever pressing to obtain a presignalized reward. The curves depict the dose-dependent lever pressing activity in spite of the warning signal preceding the punishment.

Anxiety can be induced in many other ways in experimental animals. For example, mice in an unfamiliar situation show a suppressed and fearful behaviour. Placed on an open field with holes (planche à trous) they scarcely move, and if they do so it is to explore the holes, probably to look for an escape route. They move much more freely and lose interest in searching for escape once they become familiar with the environment. Thus, when placed repeatedly on the open field, a progressively greater degree of movement results, reflecting a diminution of concern as the situation loses its novelty. Similar unconcerned behaviour can be achieved by giving the inexperienced animals a diazepine before exposing them to the strange environment (Figure 6). The same dose of the diazepine will not affect the mice when they are in a normal emotional state. This can be shown by recording their activity throughout the night. Only during the first hour, when the animals explore their novel cage and are consequently in a

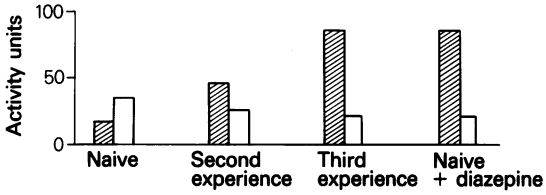


Figure 6 Activity of mice in a hole-board open field. The locomotion (number of square-crossings) and the escape exploration (number of head dippings in holes) is measured by photocells. ▨ locomotion, □ escape exploration.

hyperemotional state, is their motor activity somewhat depressed by the diazepine treatment. For the rest of the night, after the animals have returned to a normal emotional state, there is no difference in behaviour between treated and untreated individuals (Figure 7).

Sedation

In increasing doses the diazepines produce sedation, sleep and, after intravenous administration, anaesthesia. As sedation is usually considered to be a side-effect when it is anti-anxiety or anti-frustration activity which is intended therapeutically, diazepines with low sedative and high anxiolytic qualities have been called for. The question of whether the activities are separable was raised and, theoretically, it should be possible when we consider the neuronal pathways involved (Figure 8).

The reticular system controls the state of wakefulness by ascending impulses to the cortex, maintaining it in an alert condition. It receives its own input from several other systems. Vital information is transmitted via collaterals from second-order sensory neurones, e.g. from the

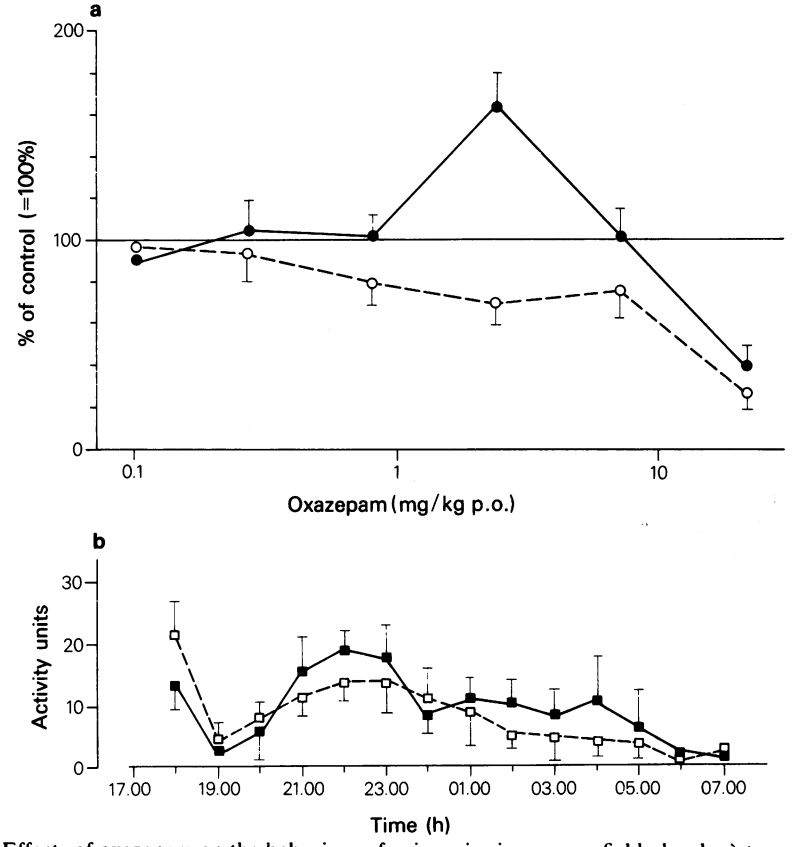


Figure 7 a) Effects of oxazepam on the behaviour of naive mice in an open field-planche à trous situation. The effects of increasing doses on locomotion (●) and hole exploration (○) are expressed as a percentage of the activity of the untreated control animals in a state of hyper-emotion and anxiety. The anxiolytic effect is reflected by the reduced exploration of the holes (way of escape) and the increased motility in the strange environment. b) Effect of a dose of oxazepam (5 mg/kg p.o., ■) exerting anxiolytic effects in the open field-planche à trous situation on the behaviour of a social group of mice during the entire night. There is no significant difference from the untreated control group (□) except for a diminished activity during the initial exploratory phase.

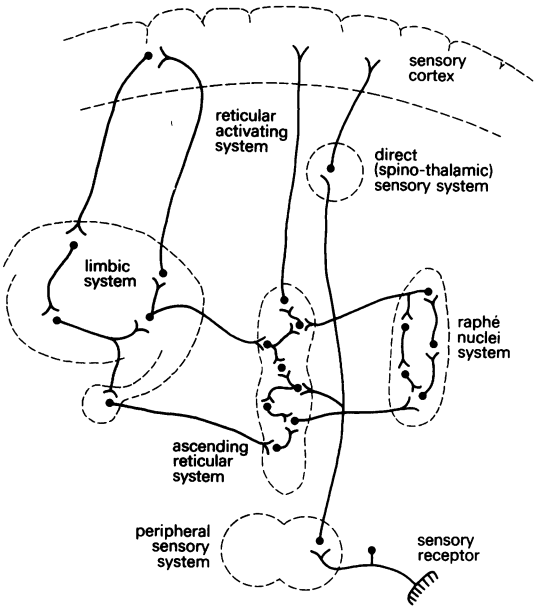


Figure 8 The ascending reticular system of the brain stem receives its input from collaterals of second-order sensory neurones. The reticular activating system consists of the neurones projecting from the upper end of the reticular formation to all areas of the cortex, alerting and enabling it to deal with information passed to the cortex along the direct sensory pathway. Furthermore the ascending reticular system can be stimulated by neurones originating in the limbic system and there is an inhibitory control by neurones from the raphé nuclei system.

spino-thalamic tract. Other stimulatory afferents, carrying information on emotional state, come from the various structures of the limbic system. Inhibitory control of the ascending reticular system is exerted by the dorsal raphé nuclei system which seems to play a role in sleep regulation.

It is obvious that a direct pharmacological suppression of the ascending reticular system would result in sedation, regardless of sensory input. Under these conditions, the state of the raphé nuclei system and the limbic system would similarly be of little influence. This means that sedation would result, regardless of the prevailing level of emotion and phase of the circadian rhythm. On the other hand, pharmacological suppression of certain parts of the limbic system would, in hyper-emotional states, prevent the arrival of stimulatory impulses at the ascending reticular system. Neurophysiological investigations have proved that, in low doses, the diazepines affect primarily the limbic system and only in higher doses additionally inhibit the reticular vigilance and arousal system (Kido *et al.*, 1966). This mode of action is typical for diazepines and not shared by other psycho-pharmacological drugs with central depressant properties (Chou & Wang, 1977; Schallek & Kuehn, 1960).

Anti-aggression

The effect of diazepines on aggressive behaviour is poorly understood despite a considerable amount of research. It has been queried whether these drugs in fact induce or inhibit aggression (Di Mascio, 1973), and it appears that both activities occur, depending on the species and the social, environmental and experimental situation concerned. According to Essman (1978) the level of social-environmental input can be of major importance in determining the action of a diazepine. For example, mice which grew up in a litter and were kept in social groups tended to exhibit aggressive responses when fed chronically with diazepines, whereas mice kept in isolation, thereby developing frustration and aggression, were rendered less aggressive by diazepine drugs.

The antiaggressive effect may in some cases have a simple behavioural explanation. Many animals show aggression because they are afraid, and in these animals the anxiolytic effect of the diazepines would prevent their aggressive behaviour. However, a primary anti-aggressive mechanism cannot be excluded, as from the neurophysiological viewpoint aggression seems to be localized in the limbic system (hypothalamus, amygdalae) which is inhi-

bited by the diazepines. Unfortunately we know little about the neurological manifestations of aggression and it is unlikely that the many types of spontaneous, reactive or laboratory induced aggressive behaviour can be attributed to one basic physiological mechanism (Moyer, 1968). It is more likely that aggressive behaviour arises from a number of very different mechanisms which we cannot expect to be influenced only by one type of drug (Valzelli, 1979).

The occurrence of aggression after administration of diazepines is not only observed in animals, but also frequently occurs in man (Shader & Di Mascio, 1970) and has been labelled as a paradoxical phenomenon, as only anxiolytic, anti-frustration and antiaggressive properties are usually considered characteristic of these drugs. However, it should be noted that aggression caused by diazepines could well be explained as a behavioural disinhibition and in this respect could be categorized psychopharmacologically together with anxiolysis and antifrustration activity.

Interaction with the functions of biogenic amines

The mechanism of action of many psychopharmacological agents is based on their interaction with certain monoamine neurotransmitters. As the diazepines exert their psychopharmacological and motor effects on neurones depending on the function of such transmitters, we must expect them to act in a similar way. However, evidence of the common types of interaction, e.g. with uptake, release, synthesis or metabolism of a biogenic amine, could not be detected. Nevertheless, as a result of the intensive research in this field which has taken place during the past ten years, claims have been made for the involvement of several biogenic amines in the mechanism of action of the diazepines, and recently gamma-aminobutyric acid has attracted particular attention.

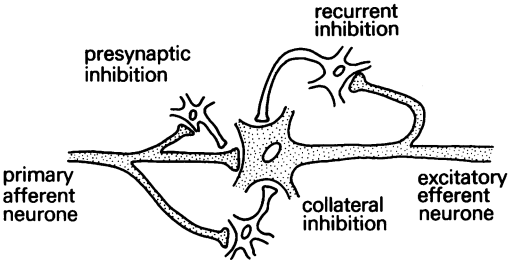
GABA

Gamma-aminobutyric acid (GABA) is now recognized as the most important inhibitory neurotransmitter in the central nervous system. Agents which block GABA-receptors or inhibit the synthesis of GABA cause hypermotor activity and convulsions. These symptoms can be prevented by diazepines, suggesting that such drugs facilitate the functions of GABA. This is not achieved by mimicking the effect of GABA at its receptor site as the diazepines have only negligible binding affinity for, and exert no intrinsic activity on, the GABA-receptor. Therefore, a less direct effect, complementing the mechanism of GABA, has to be assumed. This indirect effect has not yet been elucidated on a molecular level. On the other hand, considerable knowledge has accumulated about the inhibitory effect of GABAergic interneurones on pre- and postsynaptic excitatory neurones. Both types of neuronal inhibition are facilitated by diazepines as illustrated in Figure 9 (Polc & Haefely, 1976).

GABAergic interneurones have been shown to inhibit excitatory transmission in many pathways of the central nervous system. They are found in the spinal cord (Polc *et al.*, 1974), cerebellum (Montarolo *et al.*, 1979), cortex (Raabe & Gumnit, 1977) and various parts of the limbic system (hypothalamus: Geller & Woodward, 1979, hippocampus: Wolf & Haas, 1977), as well as in the substantia nigra (Schaffner & Haefely, 1975), the raphé nuclei (Gallager, 1978) and the locus coeruleus (Haefely *et al.*, 1976). It has been demonstrated that diazepines facilitate GABAergic inhibitory function and antagonize the effects of specific GABA-blocking agents in these neuronal systems. GABAergic neurones do not occur outside the CNS, which is in accordance with the finding that diazepines have no direct effect on peripheral somatic systems.

Glycine

Glycine is considered to be the transmitter which mediates recurrent postsynaptic inhibition of the



GABAergic inhibitory interneurones acting on an excitatory synapsis

Figure 9 Some of the principal GABAergic inhibitory pathways. In the presynaptic inhibition the GABA acting upon the terminal of a primary afferent neurone causes a decrease in the amount of excitatory transmitter released in response to an action potential. The collateral postsynaptic inhibition is moderated through the afferent, the recurrent postsynaptic inhibition through the efferent neurone. Activating the postsynaptic GABA receptor causes chloride anions to migrate into the cell increasing the negative charge of the resting potential finally resulting in a hyperpolarization. This hyperpolarization prevents the cell from being depolarized beyond the critical level so that an action potential cannot develop. Thus, the cell (postsynaptic membrane) is less sensitive to the influence of excitatory transmitters.

motor neurones in the spinal cord. The glycinergic interneurone, the Renshaw cell, is highly sensitive to strychnine which blocks its inhibitory functions resulting in overexcitation of the motor neurone and leading to convulsions. As diazepines inhibit such convulsions and also inhibit the binding of strychnine to the glycine receptor (Young & Snyder, 1973) it was proposed by Snyder and his collaborators that at least some of their pharmacological effects could be explained in terms of a stimulatory action at the glycinergic synapses. Although additional arguments supporting this hypothesis appeared (Snyder & Enna, 1975), it was strongly opposed by other authors (Curtis *et al.*, 1976, Hunt & Raynaud, 1977). In fact, the affinity of diazepines for the glycine receptor is extremely weak when compared with their affinity for the diazepine receptor. Moreover, the interactions with GABA functions, being highly specific and occurring at a much lower dose-level make action on the GABAergic system appear more likely. Further investigations which are in progress in several laboratories will clarify the role which glycine receptors may play in the various actions of diazepines.

5-Hydroxytryptamine

The anti-anxiety action of diazepines in reward-punishment conflict experiments can be mimicked by 5-hydroxytryptamine (5-HT) antagonists (methysergide, cinanserin, bromolysergic acid), 5-HT synthesis inhibitors (*p*-chlorophenylalanine) and by drugs that damage 5-HT nerve terminals (5,6-dihydroxytryptamine). Conversely, 5-HT administered intraventricularly antagonizes the anxiolytic action of diazepines (Stein *et al.*, 1975). These findings strongly suggest (a) that a 5-hydroxytryptaminergic system is involved in controlling suppressive behaviour and (b) that the diazepines may act directly or indirectly on the 5-hydroxytryptaminergic neurones of such a system. Stein *et al.* (1975) supported this hypothesis by showing that a stimulation of the (strictly 5-hydroxytryptaminergic) dorsal raphé region results in behavioural suppression and this can be reversed by oxazepam.

There is evidence that a depression of 5-hydroxytryptaminergic neurone activity by diazepines can be effected by an enhanced GABAergic output at the terminals of these neurones (Saner & Pletscher, 1979). Thus, it seems possible that the behavioural disinhibition, e.g. the anxiolytic effect, of the diazepines is produced through a GABAergic inhibition of an as yet unknown 5-hydroxytryptaminergic neurone system, whereby the behavioural suppressive activity exerted by this system is counteracted.

Dopamine

Using quantitative microspectrofluorometry, Fuxe *et al.* (1975) found that with low doses of diazepines, sufficient to release punished behaviour, a reduction of dopamine turnover in the dopaminergic parts of the limbic system occurred. It was speculated that this may have been caused by a GABAergic inhibition of the dopaminergic neurone resulting in a diminished firing rate in the ascending mesolimbic dopaminergic pathways. As we know that the diazepines exert their effects on emotional behaviour at least partially by affecting limbic structures, it could well be that the decreased dopamine turnover in these pathways is related to these effects.

Noradrenaline

A high dose of diazepam (10 mg/kg i.p.) reduces noradrenaline turnover in the cortex, probably due to a reduction of impulse flow in the noradrenergic ascending coeruleo-cortical pathways. The decreased activity of the noradrenergic cells in the locus coeruleus, which must underlie this change, is possibly mediated by an increased GABAergic input to these cells. It has been speculated that these effects on the locus coeruleus may be partly responsible for the sedation seen after the administration of diazepines (Lidbrink & Farnebo, 1973).

The stress-induced increase in noradrenaline turnover in the brain is likewise blocked by diazepines. As a state of anxiety must be considered a stress situation, it may be suspected that the anxiolytic activity of diazepines is related to their effect on noradrenaline turnover. Yohimbine, which causes anxiety in animals and man, also increases noradrenaline turnover and this action is counteracted by diazepam (Fuxe *et al.*, 1975). But there are other findings which seem to contradict such results. (−)-Noradrenaline injected intraventricularly increases the number of punished responses in a punishment-reward conflict. The effect seems to be specific as neither (+)-noradrenaline nor dopamine show this activity. Stein *et al.* (1975), who carried out these experiments, pointed out that the anxiety-reducing activity of intraventricular noradrenaline compared favourably with that of diazepines administered systemically. Unfortunately we have no further substantiation or interpretation of these interesting findings and our knowledge about the involvement of catecholaminergic neuronal systems in the mechanism of action of diazepines must be considered still very limited.

Acetylcholine

The influence of diazepines on acetylcholine functions could also be explained as being secondary to a primary effect on GABAergic interneurones which have an inhibitory action on cholinergic pathways. This is already well established for motor functions. The GABAergic presynaptic inhibition of primary afferents of motor neurones (Polc *et al.*, 1974) is an effect on an excitatory cholinergic synapse, as the motor fibres are cholinergic throughout their entire length. A GABAergic postsynaptic inhibition of motor neurones also occurs (Polc & Haefely, 1976). Moreover, an attenuation of cholinergic processes by facilitation of GABAergic inhibition could perhaps also explain the long established activity of diazepines in acting as an antidote to the toxic effects of cholinesterase inhibitors (Lipp, 1973; Rump *et al.*, 1973). It may also explain the anticonvulsant effect of diazepines against pentetrazol. This drug probably has no GABA- or glycine-antagonistic properties which could explain its convulsant activity, but has stimulatory effects on cholinergic neuronal activity, emanating from a massive release of acetylcholine (Beleslin *et al.*, 1965; Hemsworth & Neal, 1968).

In reviewing the effects of diazepines on monoaminergic systems, we can state that cholinergic, dopaminergic, noradrenergic and 5-hydroxytryptaminergic functions are depressed. It can be shown that this is usually not effected by direct action, pre- or postsynaptically, on the neurones, but is the result of a primary interaction with another neuronal system. The information available suggests that this latter neuronal system may be GABAergic in most, if not all, instances.

Effect on muscular tone and motor coordination

The central muscle relaxant action of the diazepines is based on their depressant effect on spinal and supraspinal motor reflexes (Przybyla & Wang, 1968; Tseng & Wang, 1971a, b). It has been known for some time that diazepam facilitates presynaptic inhibition in the spinal cord (Schmidt *et al.*, 1967). Some years ago, Polc *et al.* (1974) demonstrated that the effect of diazepines on presynaptic inhibition in a sensori-motor spinal reflex depends on the presence of physiological amounts of GABA. The postsynaptic inhibition in the spinal cord operates mainly through the Renshaw cell which uses glycine as a transmitter. We have already discussed the possibility of an effect of diazepines on glycine transmission. It is currently believed that in the spinal cord the reduction of motor neurone activity by diazepines, which results in muscle relaxation and disorders of motor coordination, is brought about by an activation of presynaptic GABAergic interneurones. The release of GABA at the terminals of the primary afferent motor neurone prevents its releasing the excitatory transmitter (acetylcholine) so that the motor cell in the anterior horn does not receive sufficient excitatory input.

When diazepines are used for their psychopharmacological activity, the muscle relaxant effect may be of benefit if, in hyper-emotional states, muscular tone is unduly increased. On the other hand, too much muscular relaxation, or even disturbance of motor coordination, must be considered unwanted side-effects. For this reason, diazepines which have little action on motor neurones when given in psychopharmacological dosages have been sought. Differences may exist in this respect between various commercially available diazepines, as shown by clinical experience. However, an objective experimental quantification of the effects on motor neurones exerted by psychopharmacologically active doses is difficult to achieve and has never been established. Muscular tone and coordination is usually tested in small rodents using a rotarod, climbing grid and similar methods, but the differences found in this way between substances are not convincing. More impressive dissimilarities between various diazepines are demonstrated by using high doses and testing their effects on postural reflexes. There are diazepines which hardly affect postural reflexes in animals whereas others do so in comparatively low doses. Again, the significance of such results for the effects on motor neurones in man has still to be elucidated.

The anticonvulsant property of the diazepines is certainly due to an effect on motor neurones, not only at the spinal but also at the supraspinal level. In animals, the convulsant effect of GABA receptor blocking agents, such as bicuculline or picrotoxine, is inhibited by diazepines. A GABA depletion which can be achieved by glutamic acid decarboxylase inhibitors (e.g. isoniazid or allylglycine) also results in seizures which can be prevented by diazepines. The extensor cramps caused by strychnine, which is a glycine antagonist, are inhibited to a lesser extent. All these findings seem to indicate that a facilitation of GABAergic transmission plays a major role in the anticonvulsant potency of diazepines. Nevertheless, even if one accepts this, the anticonvulsant effect of diazepines in many other kinds of seizure, not apparently related to GABA mechanisms, still requires further explanation. This applies to the antagonistic effect on seizures induced by, for example, bemegride, procaine, nicotine, harmaline, ouabain, etc, on those caused by hyperbaric

oxygen or electroshock and on those occurring on the withdrawal of drugs causing physical dependence. Finally, the diazepines are effective in experimental models of epilepsy such as the photosensitive epilepsy of baboons or the focal epilepsies developed by electrical kindling in various species.

Although the anticonvulsant activity of diazepines in so many animal models is pronounced and generally stronger than the effect of the common antiepileptic drugs, their usefulness in human epilepsy has turned out to be limited only to certain types of epileptic disease. Thus, in spite of their impressive anticonvulsant potency, the diazepines have not replaced the more classical antiepileptic drugs.

Effect on autonomic functions

Peripheral autonomic functions are not directly affected by diazepines in therapeutic doses. However, somatic manifestations of hyperemotion, which arise from influences of the limbic system on the hypothalamic control of somatic autonomic functions, may be moderated by diazepines. It is well known by clinicians that emotionally generated cardiovascular or gastrointestinal malfunctions can be restored satisfactorily by diazepines. In states of normal behaviour these drugs do not affect autonomic functions. Blood pressure, for example, is not affected in normotensive people, but is reduced in cases of arterial hypertension (Pozenel *et al.*, 1977; Masso & Perez, 1979). Such clinical findings are well supported by experimental results. Responses of somatic autonomic systems after electrical stimulation of various brain structures are strongly inhibited by diazepines, whereas in the non-stimulated animal the same autonomic functions remain unaffected. Stress-induced increases in heart rate, cardiac output, ventricular work and total peripheral resistance in dogs were significantly reduced by diazepines, whereas in the non-stressed animal there was no effect (Bergamaschi & Longoni, 1973).

The well known appetite-enhancing effect was described in the first pharmacological paper which appeared on a diazepine (Randall *et al.*, 1960). Since then, many reports have confirmed this effect in a wide variety of mammalian species. In contrast, the clinical literature rarely reports on increases in appetite caused by diazepines (Greenblatt & Shader, 1974), though there is no question that it occurs in man. Recently, the orexigenic action has been explained by a GABAergic mechanism. GABAergic neurones play an important role in the hypothalamic control of food intake (Kelly & Grossman, 1979). Muscimol injected into the hypothalamus of the rat inhibited the satiety mechanisms in the ventro-medial nucleus resulting in an increased food consumption (Grandison & Guidotti, 1977; Olgiati *et al.*, 1980). As diazepines enhance GABAergic mechanisms, they may be expected to enhance these inhibitory mechanisms resulting in an increased food consumption.

Endocrinological functions do not seem to be affected by diazepines in therapeutic doses. However, neuroendocrine reactions to emotional stress or drug action may be attenuated by diazepines. For example, the prolactinemia induced by neuroleptics is antagonized by diazepines. This is possibly a facilitatory effect on the GABAergic inhibition of the tuberoinfundibular dopamine system controlling prolactin secretion (Locatelli *et al.*, 1979).

Development of tolerance and dependence

Development of tolerance to diazepines occurs after repeated use, but this does not apply to all effects of the diazepines. It is well known that, when they are used as anti-epileptics, in a considerable proportion of the patients seizures return after several months treatment in spite of adequate dose levels (Mattson, 1972). Tolerance has also been reported in various types of animal experiments (Goldberg *et al.*, 1967). However, no clear-cut picture has so far emerged. For example, it has been stated that no tolerance develops to the anticonvulsant effect against pentetrazol in contrast to a tolerance developing to the inhibition of seizures caused by strychnine or bicuculline (Juhasz & Dairman, 1977; Lippa & Regan, 1977). In biochemical experiments, tolerance to the diazepine-induced decrease in noradrenaline turnover occurs rapidly, whereas the decrease in 5-HT turnover is maintained despite repeated doses. This parallels findings in the conflict test with rats which indicate that tolerance occurs rapidly to the central depressant (sedative) effect, whereas the anxiety-reducing effect is not diminished with repeated dosing (Margules & Stein, 1968; Stein *et al.*, 1975). In general, the literature on tolerance after long-term diazepine treatment is rather sporadic and scattered. No systematic experimental study has been carried out and no comprehensive review on this important matter is available.

Diazepines and other so-called minor tranquillizers, such as meprobamate, have dependence producing properties which have been observed in man and can be demonstrated in animals. Both 'psychic' and 'physical' dependence occur. The

signs of physical dependence are to some extent similar to the symptoms found after withdrawal from long-term use of barbiturates; furthermore, cross physical dependence can be shown between diazepines and barbiturates. Therefore, the dependence liability potential of diazepines has been classified as of the 'barbiturate type'. However, the signs of physical dependence after diazepine withdrawal are less severe than those seen with barbiturates and can only be produced after several weeks' treatment on high doses. The symptoms which have been demonstrated in monkeys include apprehension, hyperirritability, tremor, muscle rigidity, motor impairment and convulsions (Yanagita & Takahashi, 1973). A number of case reports are available which indicate that in man similar symptoms, such as anxiety, insomnia, disorientation, tremor and convulsions, can be observed upon withdrawal.

Diazepine binding sites in the central nervous system

The discovery of specific receptors for morphine stimulated the search for specific binding sites for the diazepines. This was initiated only a few years ago by the group of Braestrup & Squires (1977) in Denmark and Möhler & Okada (1977) from Hoffmann-La Roche laboratories in Basle. Binding sites were found and their highest density was in the central cortex, the cerebellum and the structures of the limbic system. The binding strength of the diazepines correlates with their pharmacological potency. Thousands of other drugs which have been tested, among them those with pharmacological similarities such as barbiturates and meprobamate, did not show affinity. The exceptions so far are the anxiolytic and hypnogenic drug zopiclone (Blanchard *et al.*, 1979), the adenosine uptake inhibitor dipyridamole (Davies *et al.*, 1980) and some anxiolytic and anticonvulsant triazolopyridazines (Lippa *et al.*, 1979).

The diazepine receptor was rendered visible by localizing the binding sites in the cell structure of the brain by electron microscope techniques (Möhler & Richards, 1980). Successful attempts have been made to isolate and identify its protein (Möhler *et al.*, 1980). Basing their theory on physico-chemical characteristics, Klepner *et al.* (1979) proposed two different receptor types for diazepines. Type I prevails in the cerebellum and is not coupled to GABA-receptors or chloride channels. Type II dominates in the frontal cortex and hippocampus and is connected with the GABA-receptor and chloride flow. There is no difference in diazepine affinity between the two receptor types, but type I binds triazolopyridazines much more strongly than does type II. It is not known whether the two types of receptors mediate different pharmacological effects. The number of diazepine receptors can be increased in stress situations (Skolnik *et al.*, 1979) and may be influenced by drugs.

In view of the close relationship which, according to the pharmacological findings, exists between the mechanism of action of diazepines and GABA transmitter functions, it would be interesting to know how the GABA- and diazepine-receptors are interconnected with each other at a cellular level. This question is currently being studied by several laboratories. The most clearcut results so far have been obtained in GABAergic interneurones of the cerebellum. It has been shown here that the diazepine binding sites are located on GABAergic neurones (Biggio *et al.*, 1980) in the regions of the 'synaptic contacts' of their nerve terminals (Battersby *et al.*, 1979; Möhler *et al.*, 1980). No decision can be made yet as to whether the diazepine receptor is located pre- or post-synaptically within the GABAergic synaptic region. A localization in the glia, which was considered, has been excluded.

The discovery of endogenous ligands for opiate receptors stimulated a search for endogenous factors which may act on diazepine receptors, perhaps displaying, for example, antianxiety, sedative or muscle relaxant activity. So far, nicotinamide and some purines have shown weak binding affinity, but their diazepine-like properties are not convincing (Möhler *et al.*, 1979). Several authors have isolated brain fractions which compete with diazepines at their binding sites, but the biological significance of these preparations is still unclear. This may also be said of the strongly binding β-carboline (ethyl-β-carboline-3-carboxylate), which was detected by Nielsen & Braestrup (1980) and seems to have anxiogenic properties (Ninan *et al.*, 1982). Thus, with the information presently at hand, we cannot make any statement on the possible existence of endogenous ligands for diazepine receptor sites.

The many agents with which diazepines have an antagonistic interaction, e.g. most of the various convulsants, do not compete with the diazepines at their binding sites. They have no affinity for the diazepine receptor so that the interaction must take place at other sites. Recently, agents which antagonize diazepines by competing at their receptor site have been discovered. These agents are imidazo-benzodiazepines. They appear to have no pharmacological activity of their own, but bind strongly to the diazepine receptor and prevent the pharmacological actions of other diazepines (Hunkeler *et al.*, 1981; Polc *et al.*, 1981). Such agents are very useful research tools but may also be of therapeutic value, for example as antidotes.

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Chemische Struktur und biologische Aktivität der Diazepine

P. DANNEBERG & K.H. WEBER

1 Seit der Einführung von Chlordiazepoxid und Diazepam ist eine Vielzahl von Diazepinen entwickelt worden. Die Anwendung dieser Arzneimittel hat seitdem immer mehr zugenommen. Ein beträchtliches Wissen über deren Wirkungsmechanismen ist inzwischen zusammengetragen worden.

2 Hier wird ein kurzer Überblick über die strukturellen und pharmakologischen Eigenschaften dieser Substanzen gegeben.

Structure chimique et activité biologique des diazépines

P. DANNEBERG & K.H. WEBER

1 Un grand nombre de diazépines a été mis au point depuis l'introduction du chlordiazépoxide et du diazépam. L'usage de ces médicaments n'a pas cessé de se répandre. On a acquis une somme considérable de connaissainces sur leur mécanisme d'action.

2 Les auteurs étudient brièvement les propriétés structurelles et pharmacologiques de ces médicaments.

Estructura química y actividad biológica de las diazepinas

P. DANNEBERG & K.H. WEBER

1 Desde la introducción del clordiazepóxide y diazepam se ha desarrollado una gran cantidad de diazepinas. El empleo de estos fármacos ha ido en aumento constante. Se ha recopilado una cantidad considerable de conocimientos sobre sus mecanismos de acción.

2 Se procede a una breve revisión de las propiedades estructurales y farmacológicas de estos medicamentos.