Dopamine Receptors and Their Behavioral Correlates
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Dopamine and Antianxiety Activity

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TAYLOR, D. P., L. A. RIBLET, H. C. STANTON, A. S. EISON, M. S. EISON AND D. L. TEMPLE, JR. *Dopamine and antianxiety activity.* PHARMAC. BIOCHEM. BEHAV. **17**: Suppl. 1, 25–35, 1982.—Clinical trials have indicated that buspirone (Buspar®) is effective in the treatment of anxiety with efficacy and dosage comparable to diazepam. Until recently it has been thought that antianxiety drugs must alter benzodiazepine receptor binding *in vitro*. However, buspirone lacks any structural similarity to the benzodiazepines and does not interact with the benzodiazepine/γ-aminobutyric acid (GABA) axis. Specifically, buspirone neither stimulates nor inhibits [^{3}H]benzodiazepine binding, does not affect the influence of GABA or halide anions on benzodiazepine binding, and does not interfere with GABA binding or uptake. Behavioral testing has revealed that buspirone does not produce muscle weakness, does not control seizures, does not potentiate the impairment of psychophysiological function or lethality produced by administration of CNS depressants, does not produce sedation/hypnosis and does not appear to possess any abuse potential or liability for physical dependence. Thus, buspirone has been termed an anxioselective agent. Buspirone appears to only interact with the dopaminergic system with reasonable potency and exhibits properties of both a dopamine agonist and a dopamine antagonist. This suggests that dopamine is implicated in the etiology and expression of anxiety. A discussion of this implication is presented with a review of the clinical efficacy of nonbenzodiazepine drugs, especially dopamine agonists and dopamine antagonists, in the management of anxiety. In addition, neuropharmacological studies which have investigated the role of dopamine in animal models of anxiety are considered. Finally, the multiplicity of dopamine receptors and their regional localization in the brain are considered in the formulation of an hypothesis which features a role for the dopaminergic agents in the pharmacotherapy of anxiety.

Dopamine Antianxiety Buspirone Pharmacotherapy

BERGER [12] has suggested two distinct types of anxiety: fear, or apprehension, and neurotic anxiety (a maladaptive response to trivial danger). Fear differs from neurotic anxiety in that in the former the victim anticipates a known danger, while in the case of neurotic anxiety the cause of apprehension may not be known. Further, in the case of neurotic anxiety the intensity of the emotion evoked frequently is greater than the threat which provokes the anxiety. Anxiety is widespread with anxiety neurosis and phobia occurring in 2–3% of the general population [106]. The 67 million prescriptions written in 1977 in the United States for chlordiazepoxide and diazepam, two popular antianxiety agents, confirm this incidence [127]. Antianxiety agents can reduce crippling anxiety, thereby facilitating problem solving and enabling the patient to cope. The pharmacotherapy for anxiety was given its impetus by the discovery of meprobamate in the 1950s but now utilizes the benzodiazepines. Although these agents are effective, the need for drugs that have fewer side effects, are more selective and exhibit less potential for abuse, has resulted in a continuing search for new antianxiety drugs. Progress in this endeavor requires a better understanding of the etiologic factors of anxiety as well as the mechanisms by which antianxiety drugs act. Pharmacologic profiles of effective antianxiety agents suggest that anxiolytic actions are mediated by γ-aminobutyric acid (GABA). Until recently, it has been thought that effective antianxiety drugs must alter [^{3}H]benzodiazepine receptor binding *in vitro*.

Historically, the relevant pharmacology of psychotropic drugs has followed from, rather than preceded, the clinical observations of therapeutic efficacy (that is, pharmacology recapitulates clinical efficacy). In this paper we shall treat the clinical observations regarding the efficacy of nonbenzodiazepines, their pharmacology and neurochemistry. Our examination of nonbenzodiazepines will not include drugs such as tricyclic antidepressants, for panic attacks, or β-adrenergic blockers, for the somatic symptoms of anxiety which have been discussed elsewhere [47]. Neuropharmacological studies which have investigated dopaminergic mechanisms will be considered in discussing a role of dopamine in anxiety.

CLINICAL PERSPECTIVE

Anxiety has been treated since early time by agents which blunt the patient's affect. Belladonna, the opiates, and alcohol were used until the barbiturates were introduced into clinical practice in 1903 [61]. These compounds produced sedation with muscle relaxation and were anticonvulsant. Meprobamate, a propanediol carbamate, was originally synthesized as a muscle relaxant in 1951, but within two years of its introduction it was widely prescribed for anxiety [11].

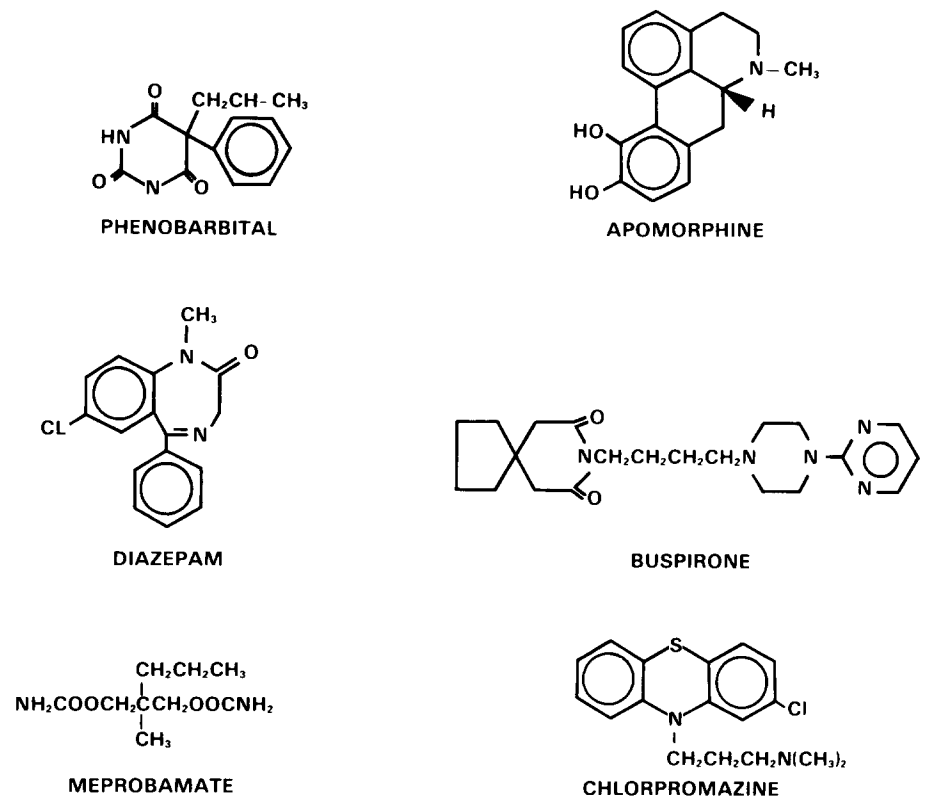

FIG. 1. Structures of drugs from representative classes which have been used in the relief of anxiety.

Meprobamate, like the barbiturates, is a sedative, a muscle relaxant, and an anticonvulsant [15]. Chlorpromazine, first used clinically in 1952, is a potent sedative. This observation led to the clinical trials of phenothiazines and other antipsychotic agents in the management of anxiety. Apomorphine in low, subemetic doses is sedating, and it has been recommended as an anxiolytic [81]. Moreover, other sedatives, such as hydroxyzine, scopolamine, tybamate, and chlormezanone, have also been used as anxiolytics [99]. The benzodiazepines were first studied clinically in 1960 for the treatment of anxiety [58] and have subsequently enjoyed tremendous success as anxiolytics. The benzodiazepines, like meprobamate and the barbiturates, are sedative, anticonvulsant, and have muscle relaxant properties. Buspirone (Buspar™ Mead Johnson Pharmaceutical Division), a new anxiolytic drug chemically unrelated to other psychotherapeutic agents (Fig. 1), lacks sedative, anticonvulsant and muscle relaxant properties [18, 54, 55, 97, 100]. Its clinical effectiveness in the management of neurotic anxiety indicates that these other activities are not an absolute requirement for anxiolytic action. This anxioselective action of buspirone and the fact that it does not interact directly with the benzodiazepine/GABA system, coupled with involvement at dopamine receptors as either an agonist or an antagonist [2, 80, 97, 98, 107, 123, 124, 125, 128, 129, 130], have led us to propose a role for dopamine in the pathology and treatment of anxiety.

The hypothesis that dopamine is implicated in anxiety receives direct support from the practice of prescribing small doses of major tranquilizers for anxiety states [41], especially in prepsychotic or borderline patients [14]. Generally, neuroleptics, which are dopamine antagonists, are minimally efficacious in the treatment of true neurotic anxiety, although they may be prescribed if the patient's symptoms are refractory to established antianxiety drugs [99]. Small doses of prochlorperazine, a phenothiazine neuroleptic, were shown in early clinical trials to be almost as effective as meprobamate or chlordiazepoxide against anxiety [75, 95, 136]. Other phenothiazines have also been used in anxiety with some success. On the other hand, other neuroleptics, including reserpine, have been studied in the treatment of anxiety with equivocal results. Occasionally, extrapyramidal side effects result from this kind of therapy [46,101].

In addition to the experience with dopamine antagonists, apomorphine, a dopamine agonist, was reported at the turn of the century to be a relaxing, sedative drug [13, 36, 37, 38, 135] which could be of value for the treatment of agitation and excitement [44]. Other investigators have subsequently noted the sedative effects of apomorphine [6, 10, 16, 25, 26, 27, 28, 30, 40, 72, 83, 115]. These effects of apomorphine can be blocked by dopamine antagonists [33]. Apomorphine not only induced sedation and relaxation in nonemetic doses but it also altered certain EEG patterns in humans and animals. Apomorphine induced changes in EEG sleep patterns in humans, which were different from those elicited by dopamine antagonists [33]. Apomorphine, piribedil, and buspirone, which all possess dopamine agonist properties, produced similar EEG profiles when analyzed by quantitative zero-cross technqiues in cats and rats. These patterns were distinctly different from those obtained with dopamine

antagonists [97,98]. Piribedil produced somnolence in parkinsonian patients [19, 78, 102], and sedation produced by piribedil in normal volunteers could be reversed by haloperidol, a dopamine antagonist [5]. In contrast, buspirone was shown to lack significant sedative/hypnotic action in clinical trials [17]. French medical practice has recognized the utility of apomorphine in the treatment of anxiety: The recommended dosage is 3 mg dissolved sublingually two to six times daily [81]. Interestingly, apomorphine is also indicated in ethanol detoxification. Several studies have shown that low doses of apomorphine can reduce the craving for alcohol in man [32, 36, 72]. One might speculate that alcohol craving is a form of self-medication for the relief of anxiety. Were this so, apomorphine's efficacy in this instance might be due to genuine anxiolytic efficacy. Benztropine, a dopamine uptake inhibitor [64,103] and thus a dopaminomimetic agent, has been shown to reduce the desire to consume ethanol [91]. Buspirone, which has been demonstrated to increase nigrostriatal impulse flow and metabolic activity of dopaminergic neurons [80], exhibited the ability to reduce the effects of alcohol detoxification in withdrawn patients without deleterious sequelae (R. E. Newton, personal communication).

BEHAVIORAL PERSPECTIVE

The term "anxiety" is used to characterize a heterogeneous cluster of psychiatric symptoms which are so poorly defined that they cannot be used to develop valid animal models which are isomorphic with the human condition. Many commentators suggest that an ideal animal model of anxiety must approach isomorphism with the human disease in terms of causation, symptomatology, and therapy. The salient features of anxiety are anxious expectation, apprehensive vigilance, motor tension, and autonomic hyperactivity [70]. A variety of animal models have been described which address themselves to certain of these features. It is not possible to clearly identify animals with anxiety; most animal models used to identify drug candidates depend upon performance measures which are affected by psychotherapeutic drugs in parallel with their clinical anxiolytic efficacy. Some models have been based upon the side effects of antianxiety drugs, e.g., muscle relaxation in the cat, antagonism of pentylenetetrazol- or electroshock-induced convulsions, or loss of motor coordination tested on a rotating rod. The models which are more likely to yield new anxioselective agents, however, include those that measure the repression of innate aggressive behavior ("taming") and the release of conditioned behavior suppressed by punishment.

The benzodiazepines were the first class of antianxiety drugs to be introduced to clinical trials on the basis of the results of animal testing. In particular, the taming of vicious monkeys by chlordiazepoxide led to its clinical trial for the treatment of anxiety [58,90]. Since then, the ability of benzodiazepines to tame monkeys has been positively correlated with clinical efficacy [119]. The taming model of Randall, used in the identification of chlordiazepoxide's anxiolytic potential, was later modified by Plotnikoff [87]. It is interesting that in this model, doses of diazepam which inhibited aggression elicited both hypoactivity and ataxia, while buspirone inhibited aggression but did not induce ataxia [134]. These observations led directly to the clinical trials of buspirone as an anxiolytic drug. It is notable that in these trials buspirone eliminated the mood scale component reflecting anger and hostility to a greater extent that did diazepam (R. E. Newton, personal communication).

TABLE 1
ANTICONFLICT ACTIVITY OF VARIOUS DRUGS

Drug	MED (mg/kg, PO)
Apomorphine	0.008*
Diazepam	0.5
Chlordiazepoxide	0.5
Buspirone	1.0
Piribedil	5.0
Tracazolate	N.A.

Anticonflict activity was determined by a modification of the Vogel drinking paradigm (Vogel *et al.* [137]). The minimal effective dose (MED) produced a significant increase in the number of licks taken in comparison to vehicle-treated rats. N.A., not active up to 20 mg/kg.

*Given subcutaneously (from Hyslop *et al.* [62]).

One of the most impressive properties of antianxiety agents in animals is their ability to release conditioned behavior which has been suppressed by punishment [76,117]. Meprobamate was shown to be active in the now-famous approach-avoidance (conflict) paradigm of Geller and Seifter [51]. The clinical efficacy of the benzodiazepines is positively correlated with their activity in this test [21]. Thus, based on the clinical efficacy of buspirone [55,100], it is not surprising that buspirone attenuated conflict behavior in rats and monkeys at doses similar to benzodiazepines, and, in contrast to diazepam, buspirone did not produce ataxia at effective doses [59, 60, 62]. However, it comes as a revelation that buspirone does not interact with GABA or benzodiazepine receptors [129]. A remarkable number of pharmacologic similarities of buspirone to apomorphine [98, 124, 125, 130] led to an investigation of the efficacy of dopamine agonists in conflict paradigms (see Table 1). Apomorphine attenuated conflict behavior in rats with a potency over 50 times greater than diazepam or chlordiazepoxide. It followed from this observation, as well as the clinical similarities noted above, that piribedil would also be active in this model of anxiety, although at much lower doses [62].

NEUROCHEMICAL PERSPECTIVE

Dopamine, in addition to being an intermediate in the biosynthesis of norepinephrine, has recently been identified as a neurotransmitter in its own right. Hence, neurochemical investigations of the actions of anxiolytics on dopamine-containing systems have only proceeded in the last fifteen years. Early preliminary studies by Corrodi *et al.* [23] showed that acute high doses of chlordiazepoxide had no effect on whole brain dopamine levels. Taylor and Laverty [131] were the first to explore the effects of benzodiazepines on the rat brain striatal dopamine system. Although striatal levels of dopamine were not affected by chlordiazepoxide or diazepam, it was suggested that uptake and reuptake of dopamine were increased in treated animals which resulted in decreased dopamine turnover. These authors showed in subsequent studies that benzodiazepines were relatively weak inhibitors of dopamine uptake and suggested that benzodiaz-

epines altered dopamine turnover by decreasing dopamine synthesis or by inhibiting dopamine release [132]. Histochemical studies have confirmed that chlordiazepoxide and diazepam reduce striatal dopamine turnover and potentiate the decreases in this turnover occurring during immobilization stress [24]. In contrast, it has been reported [45] that nitrazepam, medazepam, and clonazepam increased dopamine levels, whereas flurazepam depressed these levels, and chlordiazepoxide and diazepam were without effect. However, these latter studies were performed employing whole mouse brains which may have obscured the effects of these drugs on specific dopaminergic tracts. Doses of diazepam which are effective in the attenuation of conflict behavior caused decreases in dopamine fluorescence, indicative of decreased dopamine turnover, in the olfactory tubercle and nucleus accumbens [48]. Chronic administration of diazepam or bromazepam significantly elevated dopamine levels in rat striatum, while withdrawal from this regimen resulted in a "rebound" decrease in dopamine below control levels [93,94]. The decrease in dopamine turnover following chronic treatment was not due to decreased tyrosine hydroxylase activity [73, 92, 94]. Acute diazepam administration was shown to decrease homovanillic acid (HVA, a dopamine catabolite) levels in rat brains providing further support for a benzodiazepine-induced decrease in dopamine turnover [8].

It has been suggested that benzodiazepines decrease dopamine turnover by suppressing its functional release because chronic treatment with diazepam reduced HVA levels and withdrawal from drug resulted in elevated levels of HVA. Further, this reduction in the physiological utilization of dopamine could underlie the taming effects of benzodiazepines [93]. Benzodiazepines are known to block the elevation of HVA levels produced by neuroleptics and to decrease the rate of disappearance of dopamine caused by α-methyl-para-tyrosine [67,68]. It is well-established that dopamine agonists decrease dopamine turnover as monitored by the depression of striatal levels of l-dopa, HVA, and dihydroxyphenylacetic acid (DOPAC) [43, 77, 104, 140]. At high doses buspirone elicited an increase in dopamine turnover as reflected by increases in DOPAC levels [80,123]. However, oral administration of lower doses of buspirone which reverse trifluoperazine-induced catalepsy, decreased l-dopa levels in a manner similar to that seen with apomorphine [62, 98, 125].

Animal models have been used to investigate the mechanism of action of antianxiety drugs as well as to predict their therapeutic efficacy. Anxiolytics can affect the changes seen in brain levels of dopamine or its metabolites in models of stress. A striking decrease of dopamine was obtained in the frontal cerebral cortex of animals subjected to electric foot shock stress [133]. The ratio of DOPAC to dopamine increased in the rat frontal cortex following electric foot shock stress, and this increase was blocked by benzodiazepines [42,74]. In addition, the electric foot shock stress-induced elevation of HVA in rat cerebral cortex and striatum was blocked by diazepam [67]. The accumulation of [^{3}H]dopamine by cortical slices from mice was increased by electric foot shock immediately prior to sacrifice. Again, this increase was blocked by benzodiazepines [57, 71, 96]. In fact, animals which witnessed electric foot shock-induced fighting but were prevented from fighting themselves ("affect" controls) showed similar increases in dopamine uptake [57].

It has been proposed that the effects of benzodiazepines on dopamine turnover are secondary to actions on other neurotransmitters, especially GABA [48]. The effects of benzodiazepines on GABA and the role of this interaction in anxiety have been discussed elsewhere [86]. It has been noted that application of GABAergic agents to sites within the substantia nigra and to the terminal areas of nigral efferent neurons (output regions for striatally-mediated information) can induce behaviors resembling those observed after administration of dopamine agonists and antagonists as summarized in Table 2. In addition, GABA has been shown to modulate dopaminergic function.

For instance, striatally-mediated apomorphine-induced stereotypy was increased by the GABA agonist, muscimol, when injected into the nucleus accumbens [112]. Moreover, muscimol has been observed to strongly increase stereotyped gnawing after treatment of mice with dopaminomimetic agents such as apomorphine, cocaine, and methylphenidate. Furthermore, muscimol effectively antagonized the antistereotypic effect of dopamine antagonists on methylphenidate-induced stereotyped gnawing in a dose-dependent fashion. The benzodiazepines and barbiturates, which facilitate GABA transmission, have been shown to increase methylphenidate-induced stereotyped gnawing. In low doses these drugs potentiated the effect of muscimol on methylphenidate-induced stereotyped gnawing [108,110]. The order of potency of benzodiazepines in this regard corresponds to their affinity for the benzodiazepine receptor [122].

Conversely, facilitation of GABAergic transmission has been found to exert an inhibitory influence on dopamine-mediated behaviors elicited in the nucleus accumbens. Pycock and Horton [88] found that the hyperactive response induced by dopamine in the nucleus accumbens could be inhibited by elevations of GABA following administration of inhibitors of GABA-transaminase. Aminooxyacetic acid, a GABA-transaminase inhibitor, has been shown to antagonize hyperactivity produced by amphetamine and apomorphine [29]. Focal injection of muscimol into the nucleus accumbens was found to antagonize ergometrine-induced locomotor activity [111]. In a recent study, Pycock and Horton [89] reported that injection of GABA and the GABA agonist 3-aminopropanesulfonate into the nucleus accumbens blocked dopamine-induced hyperactivity elicited from the nucleus accumbens and inhibited increases in locomotor activity observed after systemic administration of d-amphetamine. Further, GABA receptor antagonism at low doses by bicuculline or picrotoxin enhanced the locomotor response to dopamine.

Direct administration of GABAergic agents can result in the performance of behaviors which are often referred to as being "dopamine-mediated." Bilateral infusion of muscimol or 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol (THIP) into the substantia nigra zona reticulata, entopenduncular nucleus, or subthalamic nucleus elicited a stereotyped behavior resembling that seen after systemic dopamine agonists [7, 112, 113]. A further example of GABA's involvement in dopamine-mediated behaviors is that high doses of muscimol administered subcutaneously have been found to induce catalepsy (see Table 2). Bilateral infusions of muscimol and other GABA analogues into ventromedial and ventroanterior thalamus as well as ventral striatum and ventral globus pallidus have been found to produce catalepsy, and this state was indistinguishable from that induced by dopamine antagonists [35,114]. Bilateral intranigral infusion of GABA antagonists, such as picrotoxin or bicuculline, induced

TABLE 2

BEHAVIORAL PARTICIPATION OF GABAERGIC AGENTS IN "DOPAMINE-MEDIATED" BEHAVIORS

	Induction by Dopaminergic Agents		Induction by GABAergic Agents	
Behavior	Agent	Site of Action	Agent	Site of Action
Stereotypy	DA Agonists (amphetamine, apomorphine)	Striatum	GABA Agonists (muscimol, THIP)	Substantia nigra reticulata (SNR)
			Kainic-acid-induced lesion of SNR neurons	Entopeduncular nucleus (EP) Subthalamic nucleus (STN)
Catalepsy	DA Antagonists (neuroleptics)	Striatum	GABA Agonists (muscimol, 3-amino-propane sulfonic acid, imidazolacetic acid)	Ventromedial, Ventro-anterior (VM, VA) Thalamus, Ventral Striatum Ventral Globus Pallidus
	DA Depleting Agents (reserpine, tetra-benazine) α-Methyltyrosine	Striatum		
			GABA Antagonists (picrotoxin, bicuculline)	Substantia nigra reticulata (SNR)
Rotation				
Contralateral	Direct DA Agonists (apomorphine)	Striatum (denervated side)	GABA Agonists (muscimol, THIP) Kainic-acid-induced lesion of SNR	Substantia nigra reticulata (SNR)
Ipsilateral	Indirect DA Agonists (amphetamine)	Striatum (intact side)	GABA Antagonists (picrotoxin, bicuculline)	Substantia nigra reticulata (SNR)
			GABA Agonists (muscimol)	Medial thalamic nuclei

catalepsy and prevented the induction of stereotyped behavior by apomorphine [34]. Catalepsy induced by intrathalamic administration of muscimol must be independent of dopaminergic mediation because it is not altered by high doses of apomorphine nor is it prevented by striatal or nigral lesions resulting from kainate treatment.

As a final instance, rotational behavior, commonly used to assess the potency of dopaminergic agents, can be elicited by unilateral injection of muscimol or other GABA agonists into the substantia nigra zona reticulata. GABA agonists induced contralateral turning while GABA antagonists induced ipsilateral turning [109]. Kilpatrick and his coworkers [69] found ipsilateral rotation following infusions of muscimol into the medial thalamic nuclei, the terminal area for the nigrothalamic pathway.

In addition to behavioral evidence indicating that GABA serves to modulate dopaminergic activity, it has been shown that direct microiontophoretic application of the GABA agonists muscimol and THIP directly onto zona compacta neurons in the substantia nigra *inhibits* dopamine cell firing [1,140]. However, application of GABA agonists into regions of the substantia nigra containing normally inhibitory collaterals to the zona compacta, the zona reticulata, *increase* dopamine cell firing by virtue of GABA inhibition of inhibitory synapses (disinhibition) [56,138].

Neurochemically, GABA agonists reduce dopamine turnover, resulting in increased levels of dopamine. Direct injections of GABA, γ-butyrolactone, γ-hydroxybutyric acid, or baclofen into the substantia nigra of rats increased forebrain dopamine levels [4,84]. Bicuculline, a GABA antagonist, reversed the reduction in dopamine turnover seen in rats treated with diazepam and chlordiazepoxide [48]. Thus while GABA antagonists reverse benzodiazepine-induced decreases in dopamine turnover, benzodiazepines and GABA-mimetics (aminooxyacetic acid, baclofen, γ-butyrolactone, 5-ethyl-5-phenyl-pyrrolidinone, muscimol) reversed the pimozide-induced *increase* in dopamine turnover in limbic forebrain [48, 50, 143]. GABA-mimetic agents (aminooxyacetic acid, baclofen, γ-acetylenic GABA, γ-butyrolactone) also reduced dopamine turnover in the limbic system in a fashion similar to that seen with benzodiazepines [48, 49, 85]. γ-Hydroxybutyric acid, the endogenous hydrolyzed form of γ-butyrolactone, both increased dopamine synthesis and decreased dopamine utilization [3]. However, other laboratories have reported that systemic treatment with aminooxyacetic acid or γ-butyrolactone stimulated striatal and cortical tyrosine hydroxylase and elevated l-dopa, DOPAC, and dopamine levels in the olfactory tubercle [105,139]. Furthermore, it has been reported that intranigral muscimol significantly increased levels of HVA and DOPAC in the striatum [108]. GABAergic compounds also effect the release of dopamine from dopamine cells.

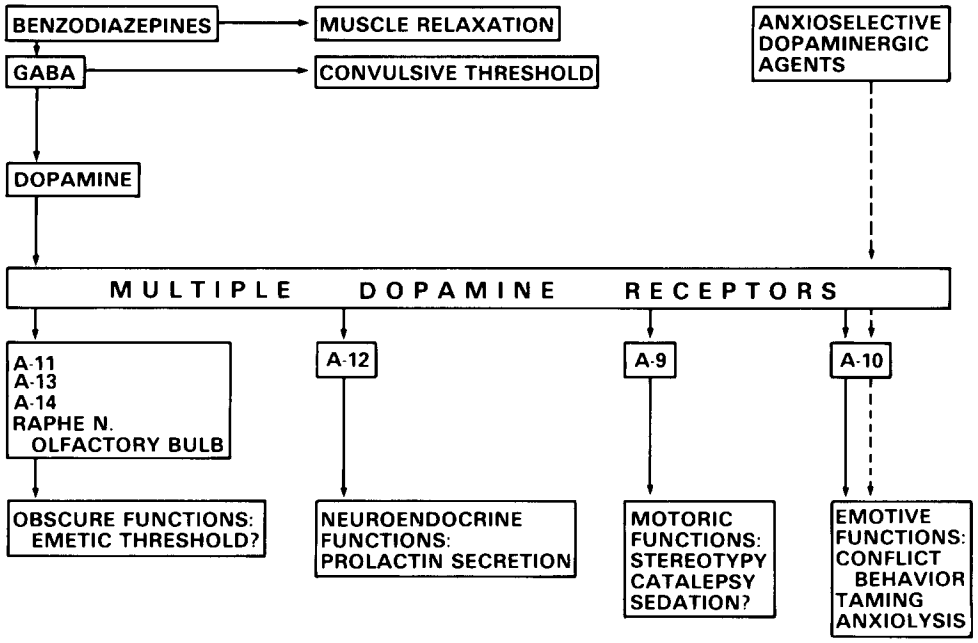

FIG. 2. Hypothetical pathways by which anxiolytic drugs achieve the various actions attributed to them. The A-11, A-13, and A-14 cells are located in the caudal, dorsal, and anterior hypothalamus, respectively. The A-12 cells are part of the tuberoinfundibular pathway. The A-9 cells belong to the nigrostriatal pathway. The A-10 cells have terminals in the mesolimbic areas (n. accumbens, olfactory tubercle, septal nuclei, amygdala) and mesocortical areas (cingulate cortex, entorhinal cortex, and frontal cortex: medial wall and rhinal fissure). Reproduced with permission from D. P. Taylor, L. A. Riblet and H. C. Stanton. *Anxiolytics: Neurochemical, Behavioral and Clinical Perspectives*, edited by J. B. Malick, S. J. Enna and H. I. Yamamura. New York: Raven Press, 1982.

Activation of GABA transmission by systemic administration of GABA and GABA agonists induced release of dopamine in the striatum [20,39], and GABA was found to stimulate DA release *in vitro* in striatal or nigral slices [53,126]. However, SL 76 002 also reversed increases in striatal and limbic dopamine turnover induced by haloperidol, butaclamol, and sulpiride [9]. Thus, while discussing the role of GABA in benzodiazepine-induced anxiolysis, the complex GABA-dopamine interaction must be considered.

ANXIOSELECTIVE ACTION WITH DOPAMINERGIC AGENTS

Cools and Van Rossum [22] have attempted to characterize dopaminergic receptors based initially on brain location, i.e., excitation-mediating receptors occur in the rat neostriatum while inhibition-mediating receptors occur in the nucleus accumbens. Creese and his associates [31] suggested that striatal dopamine receptors might interconvert between agonist- and antagonist-preferring conformations, thus explaining the data obtained with *in vitro* radioligand binding experiments. Spano *et al.* [121] noted the biochemical heterogeneity of dopamine receptors, which led to the classification schemes of Kebabian [65] and Kebabian and Calne [66]. The clinical evidence for multiple dopamine receptors in man has been reviewed [82] and, at this time, classification schemes for at least four dopamine receptors have been put forward [116,120]. These schemes have, in general, rested strongly upon the varying effects of dopamine antagonists, but it is known that multiple and/or biphasic responses to dopamine agonists are also possible [52,118]. Thus, two types of response to a drug are possible: (1) A drug may interact at one type of receptor but not at another, where the characterization of type is by location or biochemical coupling. (2) A drug may act at one dose, biochemically or behaviorally, as an agonist, while at higher doses it could behave as an antagonist.

One of the major pathways by which dopamine influences behavior is the mesolimbic-mesocortical fiber system (A-10 cells originating in the ventral tegmental area projecting to the nucleus accumbens, septum, olfactory tubercle, and amygdala, in addition to the cortex). Broadly speaking, this pathway is responsible for the behavioral, "emotive" as opposed to motor or neuroendocrine, functions of dopamine [79]. Iversen [63] has suggested that dopamine in the forebrain is important to the ability of an organism to focus on, and come under the control of, relevant stimuli in the environment. We have discussed the interactions between benzodiazepines and dopamine in various animal models of anxiety. These interactions suggest that the mesocortical dopaminergic system plays a role in the cerebral circuitry of emotionality and that the benzodiazepines modulate this in some manner. Benzodiazepines facilitate GABAergic neurotransmission which in turn may activate dopaminergic systems [49]. In the case of buspirone it appears that an anxioselective action may be achieved through differential interaction at the multiple dopamine receptors occurring in

TABLE 3
PHARMACOLOGIC PROPERTIES OF ANXIOLYTIC DRUGS

Property	Propanediol carbamates	Benzodiazepines	Buspirone
Date of First Clinical Trials	Early 1950s	Late 1950s	Late 1970s
Clinical Efficacy	+	+	+
Conflict Attenuation	+	+	+
Monkey Taming	+	+	+
Sedation/Hypnosis	+	+	−
Muscle Relaxant	+	+	−
Anticonvulsant	+	+	−
Interaction with CNS Depressants	+	+	−
Physical Dependence Liability	+	+	−
Abuse Potential	+	+	−

+ = Property present; − = property absent.

different locations in the central nervous system. We have developed a diagrammatic model which serves to explain our hypothesis (Fig. 2). In this hypothesis some of the modulatory influences of benzodiazepines on GABA neurotransmission would be expressed *via* dopaminergic pathways which mediate a variety of functions such as ataxia, conflict-reward interactions, and anxiolysis. Anxioselective agents, such as buspirone, may preferentially act at subclasses of dopamine receptors residing in the mesocortical and possibly mesolimbic pathways. Ancillary dopamine-mediated effects would result from agonist or antagonist actions at other dopamine receptors. Thus, as illustrated in Table 3, buspirone preferentially affects those systems responsible for anxiolytic/anticonflict actions without appreciably eliciting other actions such as sedation, muscle relaxation and anticonvulsant effects. In contrast, the less selective propanediol carbamates and benzodiazepines affect all of those systems. Based on this conception and using buspirone as an example of an anxioselective dopaminergic agent, we have investigated the possibility that a higher degree of selectivity is available. Although the preclinical data obtained are promising, confirmation awaits the verdict of clinical trials [142].

The advent of antianxiety drugs which may act indepedently of benzodiazepine receptors has been a stimulus for reassessing theories relating to the mechanisms of action of antianxiety drugs and the neurochemical abnormalities associated with this disorder. The clinical efficacy of buspirone in the management of anxiety [55,100] suggests that dopamine is implicated in the etiology or expression of anxiety. Dopamine and dopamine modulating drugs are seldom discussed in anxiety or its treatment. It is hoped that a new perspective arising from the concept that dopamine is important could result in new strategies for anxiolytic drug development.

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