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COMMUNICATIONS

A common structural basis for c.n.s. drug action

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The importance of an aromatic ring and a nitrogen atom in most central nervous system (c.n.s.) active drugs has long been recognized, and specific topographical arrangements of these groups have been proposed as basic requirements for analgesic (Beckett & Casy 1954; Feinberg et al 1976; Gorin & Marshall 1977), antipsychotic (Horn & Snyder 1971; Humber et al 1979; Tollenaere et al 1980), antidepressant (de Paulis et al 1978; Maxwell & White 1978), hallucinogenic (Baker et al 1973; Kang et al 1973), anticonvulsant (Andrews & Lloyd 1982) and stimulant (Grunewald et al 1979a) activities. The seemingly fundamental role of the aromatic ring and the nitrogen atom *within* each of these drug classes led us to ask: what are the differences in the topographical arrangements of these groups *between* different c.n.s. drug classes?

As an initial approach to this question, we have compared the crystal structures of the recognized representative compound from each of eight major c.n.s. active drug classes, viz, chlorpromazine (antipsychotic, McDowell 1969), imipramine (antidepressant, Post et al 1975), amphetamine (stimulant, Bergin & Carlström 1971), LSD (hallucinogen, Baker et al 1973), diazepam (anxiolytic, Camerman & Camerman 1972), phenobarbitone (hypnotic, Williams 1973), diphenylhydantoin (anticonvulsant, Camerman & Camerman 1971), and morphine (analgesic, Gylbert 1973). Of these, morphine and LSD are relatively rigid structures, and it may be assumed that their crystal structures approximate their biologically active conformations. The other molecules all have one or more degrees of conformational freedom, and their crystal structures may or may not represent the biologically active forms. It is known, however, that the conformations observed in the crystals are also among the low energy solution and isolated state conformations for each of these eight molecules, and the available rigid analogue data are consistent with the observed crystal structures (Andrews & Lloyd 1982).

The molecular comparisons were done using the molecular modelling system, MORPHEUS (Andrews & Lloyd 1982), by least squares minimization (Andrews 1979) of the distances between corresponding key atoms in the eight molecules, thus optimizing the overlap of the aromatic rings and nitrogen atoms. In molecules with more than one aromatic ring or nitrogen atom, each of the alternative combinations was considered and the best superimposition chosen. Perspective views of the drugs in this common orientation are shown in Fig. 1, and all eight molecules are superimposed in Fig. 2. It is immediately apparent that there is a remarkable consistency in the topographical arrangement of the nitrogen and aromatic moieties in the solid state conformations of this series of structurally and functionally diverse molecules.

It is also apparent that the aromatic moieties of these drugs are all capable of forming van der Waals' interactions with a planar receptor surface, but the nature of the common nitrogen atom varies from basic (e.g. amphetamine) to neutral (diazepam) or acidic (phenobarbitone). However, the relevant pK_a values (Bowman & Rand 1980; Wolff 1981; Foye 1981) show that in the forms which predominate under physiological conditions, the common nitrogen, whether charged or not, is always able to donate a proton. The topographical similarities observed across the series thus indicate that all of these molecules could have a *common* structural basis for their c.n.s. drug action.

If this proves to be the case, then the common aromatic ring and nitrogen atom cannot be held responsible for *distinguishing* different classes of activity (antipsychotic, analgesic, etc.). Rather, these must be due to the nature of additional binding groups, and their placement relative to the common groups. Accessory binding groups that are known to be implicated in c.n.s. activity include an additional aromatic ring (imipramine, Grunewald et al 1979b), alkyl substituent (amphetamine, Grunewald et al 1979a), polar group (morphine, Gorin & Marshall 1977) or halogen atom (chlorpromazine, Humber et al 1978).

On the basis of these observations, we put forward the following working hypotheses:

1. There is a common structural basis for the activity of many different c.n.s. active drug classes.
2. The aromatic ring and nitrogen moieties are the primary binding groups whose topographical arrangement is fundamental to the activity of these drug classes.
3. It is the nature and placement of secondary binding

* Correspondence

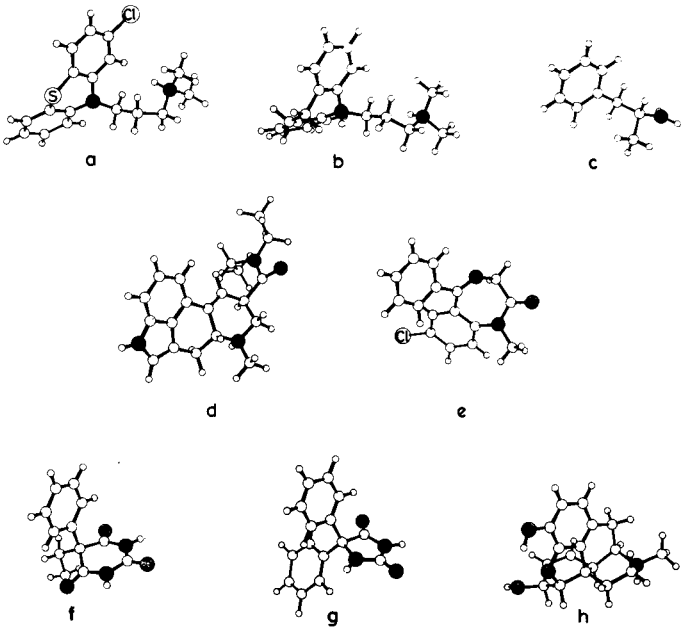

FIG. 1. Perspective views of representative compounds from major c.n.s. active drug classes (a) chlorpromazine, (b) imipramine, (c) amphetamine, (d) LSD, (e) diazepam, (f) phenobarbitone, (g) diphenylhydantoin, (h) morphine. Light and dark shadings represent oxygen and nitrogen atoms, respectively.

groups that determines different classes of c.n.s. drug activity.

A general consequence of these proposals is the expectation that c.n.s.-active drugs will frequently interact with more than one neurotransmitter system in the c.n.s. That this is indeed the case is increasingly evident both from binding studies (Stone 1974; Closse et al 1981) and in the discovery of novel c.n.s. activity in established structural classes of c.n.s. drugs. Recent examples include analgesic benzodiazepines (Römer et al 1982) and enkephalin analogues with antipsychotic activity (Coy & Kastin 1980).

In most cases the same topography is apparent in the structure of associated neurotransmitters (Andrews & Lloyd 1982), although *both* primary binding groups are not always required for neurotransmitter activity. GABA, glycine and acetylcholine, for example, each lacks an aromatic ring. The presence of a residual aromatic binding site in the receptors for these neurotransmitters is implied, however, by the structure of the antagonists bicuculline, strychnine and procyclidine, respectively. A similar situation may apply to those c.n.s. active drugs which lack a nitrogen atom (e.g. cannabinoids) or an aromatic ring (e.g. meprobamate). Alternatively, isoelectronic or isosteric groups in these structures may substitute for the nitrogen or aromatic moieties.

These observations lead us to the intriguing possibility of an evolutionary pathway from a single primaeval transmitter molecule with its associated receptor to the whole class of c.n.s. neurotransmitters with their

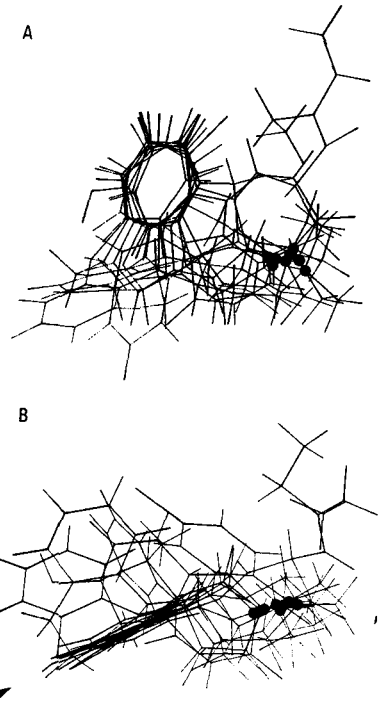

FIG. 2. (A) Superimposition of all eight molecules with the same perspective view points as in Fig. 1. (B) Fig. 2(A) viewed side-on to the aromatic groups (arrowed). The common nitrogen atoms are indicated (•).

structurally and functionally specific binding sites. The available phylogenetic evidence suggests that either acetylcholine (Michelson & Zeimal 1973) or an aromatic amine (Krnjević 1974; Gerschenfeld 1973: Roth et al 1982) could fulfil this role as the oldest of the known neurotransmitters. A related evolutionary process could apply to the enkephalins and other c.n.s. active peptides, many of which contain an *N*-terminal tyrosine that can potentially adopt a similar topographical arrangement of the common binding groups (Gorin & Marshall 1977).

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