Some New Behaviour-disrupting Amphetamines and their Significance

by
J. R. SMYTHIES
V. S. JOHNSTON
R. J. BRADLEY
Department of Psychiatry,
University of Edinburgh

F. BENINGTON
R. D. MORIN
L. C. CLARK, jun.
Department of Psychiatry and Surgery,
Medical College of Alabama,
Birmingham, Alabama

The effect of a series of amphetamines has been investigated, and the results suggest that substitution in the para- position is important for hallucinogenic properties.

AMPHETAMINE is the paradigm of a central stimulant drug, and it is also known to cause a paranoid psychosis closely resembling a schizophrenic illness in certain addicts. Peretz *et al.*[1] first reported that a derivative of amphetamine—3,4,5-trimethoxy amphetamine—was hallucinogenic in man. Its effects were very similar to those of its close chemical relative mescaline. Smythies *et al.*[2] have developed a behavioural test for animals, based on the Sidman Avoidance Schedule and the Bovet-Gatti profiles, which has proved to be reliably predictive of the hallucinogenic effect of a drug on man. We used this test to show that of the nineteen possible methoxylated phenylethylamines, only three were active in disrupting behaviour—the 3,4,5 compound (mescaline itself), the compounds 2,3,4,5 and 2,3,4,5,6, in order of increased activity. All the other 16 were inactive. Thus it appears that for hallucinogenic activity, at least 3 methoxy groups are required, and that these had to be in the 3,4,5 configuration. The two other active compounds were more lipid-soluble than mescaline, and are not metabolized by amine oxidase; mescaline being metabolized by diamine oxidase but not by monoamine oxidase.

In this present investigation, we have examined the following series of methoxylated phenylisopropylamines (amphetamines): the 3,4,5, 2,4,5, 2,4,6 and 2,3,4 trimethoxy compounds; the 2,3, 2,5, 3,5 and 3,4 dimethoxy compounds; and the 3 monomethoxy derivatives 2, 3, 4. Each compound was tested on two animals exactly as described in our previous communication[2]. The results in this series were quite different from those in the ethylamine series.

In the trimethoxy amphetamines activity was in decreasing order: 2,4,5 > 3,4,5 > 2,4,6 $\gg$ 2,3,4. A typical Bovet-Gatti hallucinogenic profile was obtained for the first three, whereas the 2,3,4 compound was almost inactive. A very similar result was obtained in human studies by Shulgin[3], who found the 2,4,5 compound to be seventeen times as active a hallucinogen as mescaline, the 3,4,5 compound to be approximately twice as active, and the 2,3,4 compound to be inactive.

In the dimethoxy series, we found the 2,3, 2,5 and 3,5 compounds to be inactive, but the 3,4 compound was highly active, 12·5 mg/kg being roughly equivalent to 25 mg/kg mescaline.

The monomethoxy series was the most interesting. The ortho-compound showed moderate amphetamine-like activity over a wide dose range.

Para-methoxy amphetamine (PMA), however, proved the most potent hallucinogen we have so far tested (with the exception of LSD). In a dose of 3·1 mg/kg, it produced a typical "low dose hallucinogenic" Bovet-Gatti profile, quite distinct from the Bovet-Gatti profile for amphetamine. In doses of 6·2 mg/kg, it disrupted bar-pressing behaviour completely, and induced bizarre behaviour in both the rats tested. Although the rat could walk about normally, and appeared to be able to eat and drink normally, it frequently walked backwards—a typical mescaline effect. It would show exaggerated startled responses in the absence of external stimuli and would frequently engage in strange behaviour reminiscent of shadow boxing—rearing and pawing in the air. If placed on a table, it would walk apparently normally towards the edge and fall off, and would do this repeatedly if replaced on the table. This period of abnormal behaviour lasted one day in one rat, when the animal died, and one week in the second rat, when this animal also died.

Thus the present data would suggest that the essential feature of the "hallucinogenic" molecule in this series is the para-methoxy group. All compounds lacking this were inactive and compounds with additional groups were variously weaker. The different results in the phenylethylamine series may be due to the fact that the apparently inactive compounds may be too easily oxidized by amine oxidase to produce behavioural effects following parenteral injection. It is known that the 3,4-dimethoxyphenylethylamine is a much better substrate for amine oxidase than is mescaline[4,9]. Once the molecule is protected from amine oxidase by α-methylation, then the behavioural reaction to the drug, injected parenterally, may more truly reflect activity at the site of action. To test this hypothesis, we pretreated an animal with 50 mg/kg iproniazid 3 h before injecting 6·2 mg/kg of para-methoxyphenylethylamine (PMPEA)—which is also *o*-methyl paratyramine. Neither of these given alone produced the slightest effect on behaviour, but when they were given together, behaviour was completely disrupted and toxic effects rapidly appeared: the rat lay on its side twitching slightly, and died in a few hours. The same dose of iproniazid given before injecting 12·5 mg/kg mescaline increased the effect of mescaline only two-fold and no toxic effects appeared[5]. This experiment is being repeated with lower dosages of PMPEA. This increase in the toxicity of 4-methoxyphenylethylamine following MAO has also been reported to produce an intense rage reaction and hyperthermia in cats[10]. It has also been found that para-methoxy amphetamine at 25 mg/kg was lethal in cats after producing a similar rage reaction.

The severe and prolonged disruption of behaviour produced by PMA suggests an irreversible inhibition of an enzyme—possibly catechol *o*-methyl transferase. Because 3-methoxylation is the normal method of inactivating catechol amines, it seems not impossible that catechol *o*-methyl transferase might be blocked, or its action distorted in some way, by 4-methoxylated phenylethylamines or isopropylamines. A second hypothesis is that because amphetamine is usually para-hydroxylated in the rat, the interference with this reaction by the para-methoxy group might have behavioural results.

Thus it would be of interest to analyse by biochemical and pharmacological techniques the mechanisms of action of PMA. The action of PMA on species that do and do not

parahydroxylate amphetamine would also be of interest. Human testing with PMA would clearly require great care. The potent and long lasting hallucinogen STP has been identified as a derivative of dimethoxy amphetamine.

Finally, these findings suggest the hypothesis that schizophrenia may be associated with 4-methoxylation of catecholamines or of tyramine, or with some disturbance in whatever biochemical mechanism is affected by these paramethoxylated compounds. In this respect, the recent reports by Boulton *et al.*[7], that one "pink spot" excreted by schizophrenics is paratyramine, and by Jenner *et al.*[8], that a manic depressive patient was excreting very large amounts of paratyramine metabolites, are of interest. Our data suggest: (1) that *o*-methyl paratyramine produced in the synapse (separated from MAO) would have profound and long lasting effects on behaviour, and that the fact that 3,4-dimethoxyphenylethylamine (DMPEA) is inactive in humans on parenteral injection may be due to its rapid breakdown by MAO, and that it also might disrupt behaviour if locally produced in the synapse; and (2) that the psychosis found in amphetamine addiction may be associated with the production of 4-methoxy amphetamine

This work was supported by a grant from the Medical Research Council.

Received August 7, 1967.

[1] Peretz, D. I., Smythies, J. R., and Gibson, W. C., *J. Ment. Sci.*, **101**, 317 (1955).
[2] Smythies, J. R., Johnston, V. S., Bradley, R. J., Benington, F., Morin, R. D., and Clark, L. C., *Psychopharmacologia*, **10**, 379 (1967).
[3] Shulgin, A. T., *Nature*, **201**, 1120 (1964).
[4] Hollister, L. E., and Friedhoff, A. J., *Nature*, **210**, 1377 (1966).
[5] Smythies, J. R., Bradley, R. J., and Johnston, V. S., *Nature*, **215**, 1179 (1967).
[6] Iversen, L. L., *Nature*, **214**, 8 (1967).
[7] Boulton, A. A., Pollitt, R. J., and Majer, J. R., *Nature*, **215**, 132 (1967).
[8] Jenner, F. A., Gjessing, L. R., Cox, J. R., Davies-Jones, A., Hullin, R. P., and Hauna, S. M., *Brit. J. Psychiat.*, **113**, 895 (1967).
[9] Benington, F., Morin R. D., and Clark, jun., L. C., *J. Medicinal Chem.*, **8**, 353 (1965).
[10] Benington, F., Morin, R. D., and Clark, jun., L. C., *Alabama J. Med. Sci.*, **4**, 417 (1964).

Inertial Confinement of Extended Radio Sources

by
DAVID S. DeYOUNG
Center for Radiophysics and Space Research,
Cornell University,
Ithaca, New York

W. I. AXFORD
Departments of Physics and Applied Electrophysics,
University of California,
San Diego, La Jolla,
California

The confinement of extended radio sources may be a dynamic rather than a static process where the internal pressure of the source is balanced by the ram pressure of the intergalactic gas.

In this article, we discuss the nature of those strong radio sources in which the radio emitting regions are separated from the parent object by distances comparable with or greater than the dimensions of the sources. These radio sources are often double, with the parent object (commonly a giant elliptical galaxy) situated between the sources and roughly at their centroid. Descriptions of such sources, of which Cygnus *A* is a well known example, have been given by Maltby, Matthews and Moffet[1] and by Burbidge, Burbidge and Sandage[2].

Apart from information concerning the radio spectra, present observations of strong radio sources provide little more than the luminosities and approximate dimensions of the components, although with higher resolution studies now becoming possible it seems that a certain amount of fine structure can be observed. In the case of Cygnus *A* the emitted power in the radio frequency range is estimated[1] to be $4{\cdot}4 \times 10^{44}$ ergs/sec, with the two (approximately equal) components separated by about 79 kparsec and having diameters of about 35 kparsec. From such information the usual procedure is to estimate the minimum total energy, E_{min}, in particles and the magnetic field required to produce the observed luminosity by the synchrotron mechanism. Thus, for Cygnus *A*, if the energy densities of relativistic electrons and nuclei are equal, and if the magnetic field fills the emitting volume uniformly, the minimum energy is of the order of 3×10^{59} ergs, and the corresponding magnetic field strength, H_0, is about 7×10^{-5} oersted[1,2]. If the magnetic field fills only a fraction, f, of the volume of the source, then the energy required decreases by a factor $f^{3/7}$ and the magnetic field increases by a factor $f^{-2/7}$; for example, if $f = 10^{-2}$, then $E_{min} \approx 2 \times 10^{60}$ ergs and $H_0 \approx 3 \times 10^{-4}$ oersted. For sources other than Cygnus *A*, similar calculations imply $E_{min} \approx 10^{57}$–10^{61} ergs and $H_0 \approx 10^{-6}$–10^{-4} oersted.

The significance of these calculations is limited by their over-simplification of the problem. Nevertheless, an important result is implied, namely, that the internal pressure of the emitting region is at least $H_0^2/8\pi$. The actual pressure might exceed this value considerably, for a comparable pressure must be exerted by the energetic particles involved, and the configuration need not correspond to the minimum energy configuration for the observed luminosity. One would also expect the emitting regions to be roughly in hydrostatic equilibrium in a co-moving frame of reference so that regions of high magnetic pressure tend to have low particle pressure and vice versa. To maintain the pressure within such an object (hereafter called a "plasmon", a term introduced in a slightly different sense by Shklovskii[3]) which is well separated from its source and presumably in near equilibrium with its surroundings, an external confining pressure of at least $H_0^2/8\pi$ is necessary.

It has been suggested that the confinement could be provided by an intergalactic magnetic field, and that such a field would also produce the observed alignment of the plasmons with the object from which they have been ejected[4]. This would require an intergalactic field strength at least equal to the minimum value of H_0 required for any observed source of the type under discussion. That is, the intergalactic field would have to have a strength $H_m \geq 7 \times 10^{-5}$ oersted, as deduced for Cygnus *A*. The pressure exerted by the intergalactic magnetic field, however, should not exceed the total pressure of the interstellar medium in our own galaxy, which implies that H_m is less than about 1×10^{-5} oersted. This is probably a gross overestimate of H_m (ref. 5), but it is none the less far too small to confine and collimate the Cygnus *A* plasmons. Moreover, if the intergalactic field were the confining agency, the pressure inside all similar objects would be the same (that is, $H_m^2/8\pi$), and there is no reason to believe that this is the case.

With essentially the same arguments, one is led to reject the possibility that the confinement is due to the static pressure of the intergalactic gas in a "hot" universe, a conclusion which is also implied by observations of the