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Adrenochrome as a psychotomimetic agent.
A review of the literature

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The potential physiological importance and pharmacological activity of catecholamine oxidation products, such as adrenochrome, has attracted the attention of researchers for many years. However, it is only in recent years that pure and stable samples of these compounds have become readily available and this has facilitated the development of pharmacological work in this field. However, unless certain precautions are taken, adrenochrome, prepared by the usual procedures, will contain variable amounts of its rearrangement product adrenolutin, insoluble melanin-like products and some residual pigment (1).

In instances where solutions of oxidised adrenochrome have been used for pharmacological studies, without preliminary isolation of adrenochrome, some of the results obtained may be open to question since such solutions probably contained some unchanged adrenochrome, as well as other unidentified oxidation products of adrenochrome.

A study was carried out by HEACOCK et al. in 1963 on the stability of adrenochrome in the dry state and in solution and on the purity of various commercial samples of this compound. The results reported by this team of investigators should be employed when interpreting results of biological studies using either adrenochrome samples that are more than one year old, or some of the commercially available samples of this substance (2). It was further pointed out that pharmacological results could be invalidated if the adrenochrome solutions being examined were contaminated by trace quantities of metallic ions (2).

KIRCH was one of earlier workers to be interested in the physiological activity of oxidised adrenochrome (1950), which he referred to in 1930 as "omega" substance (3). The possible pharmacological role of "omega" has now been known to be adrenochrome was first observed by KIRCH in 1930 and later confirmed by BACQ and BACQ (5). The general pharmacology of adrenochrome has been reviewed by several workers including; KIRCH (4), MARQUARDT (6), BACQ (5), TATTA (7), SCOTTI (3, 8), HOFFER (9), and HOFFER and OSMOND (10).

The psychotomimetic effects ascribed to adrenochrome and the possible role of this compound in the etiology of some forms of mental illness, particularly schizophrenia, have been the subjects of some controversy since the adrenochrome hypothesis of schizophrenia was originally proposed by HOFFER, OSMOND and SCOTTI in 1954 (11). This hypothesis resulted in part from the suggestion made two years earlier by OSMOND AND SCOTTI that schizophrenia might result from an alteration in the normal metabolism of adrenochrome in the body resulting in the formation in vivo of a psychotopic metabolite of adrenochrome (12). OSMOND and SCOTTI referred to this hypothetical substance as "mescaline-like" physiological activity (12). These authors were impressed with the relative similarity of the chemical structures of adrenochrome and mesaline and there appeared to be some reasonable possibility that the unknown adrenochrome derivative might be endowed with mesaline-like psychotomic activity (12). In the later paper HOFFER et al. hypothesised that adrenochrome was a suitable candidate for a "M-substance" (11). This suggestion was based on the results of self-administration of adrenochrome and found that when psychotic reactions had occasionally occurred when a "deteriorated" or "pink" adrenochrome was used in anesthetized and conscious subjects (10, 11). HOFFER and OSMOND later documented a specific case in which one subject experienced a prolonged psychotic reaction after inhaling a "coloured" adrenochrome solution for a six hour period (13). In 1957 HOFFER reported that adrenolutin, in doses of 25-50 mg, also produced psychological changes in human volunteers (9, 10, 14). MELANDER and MARTENS also showed that adrenochrome administered at a dose level of 100 mg produces catatonia in cats (17).

The basic assumptions upon which the adrenochrome hypothesis of schizophrenia are based, and which would have to be proved to be true before the hypothesis could be accepted are: (i) adrenochrome (or some readily derivable compound, such as adrenolutin) is psychotomimetic in man; (ii) adrenochrome and adrenolutin could be metabolites of adrenaline in man under certain circumstances; and (iii) adrenochrome formation and metabolism is disturbed in schizophrenia (cf. HEACOCK and HOFFER (18), HOFFER and OSMOND (19)). With reference to the last point HOFFER has suggested that adrenochrome is a normal metabolite of adrenaline and that it can be metabolised in two ways. One pathway leads to the formation of adrenolutin 2, which is considered to be a toxic substance and the other pathway leads to the production of 5,6-dihydroxy-N-methylindole 5 which is reported to be non-toxic (18).

Schizophrenia results when the normal balance between these two pathways is upset (18). There is evidence to suggest that two major metabolic pathways exist in certain individuals for adrenochrome, one involving rearrangement to adrenolutin 2 and the other leading to the formation of 5,6-dihydroxy-N-methylindole 5. As a result of studies involving the use of labeled adrenochrome, NOVAL et al. reported in 1962 that adrenochrome I is metabolised in rats to give what is probably a sulphone conjugate (14). The sulphone product is highly fluorescent and relatively unstable and two derivatives of 5,6-dihydroxy-N-methylindole, probably sulphate and glucuronide conjugates (21). Similar products can also be detected in the urine of rats which have been fed adrenochrome or 5,6-dihydroxy-N-methylindole in place of adrenochrome (21). These findings effectively undermined the earlier work of FISCHER and LECOTTE (22); BACQ, FISCHER and LECOTTE (23); and FISCHER and LECOTTE (24). However both NOVAL et al. (21) and the earlier Belgian workers (22, 23, 24) found that there were certain species differences. For instance FISCHER and LECOTTE reported that in the cat and the dog, both the administered adrenochrome was excreted unchanged, whilst in rabbits the main product was adrenolutin, both free and as a sulphate conjugate (24). SCHAEFER and SMOLY also reported that adrenochrome was metabolised by rats to an unstable yellow pigment (25). It is most probable however that extensive decomposition of this pigment occurred in the systems used during the course of chromatographic investigations (cf. NOVAL et al. (21)).

The adrenochrome hypothesis of schizophrenia is discussed at length in a series of publications by HOFFER and OSMOND (10, 11, 14-16, 18, 19, 26-30). Some workers, including BENJAMIN (31), SYMTHS (32, 33), KETY (34) and SOURKIS (35, 36), have however been critical of this hypothesis. HOFFER et al. in 1954 were the first to report that adrenochrome gave rise to psychotomimetic effects in man (11). These workers observed effects from doses (i.e. 1 mg) in the 0.5 to 10 mg range including marked effects from doses as low as 0.5 mg. In the same year RINKE, SYMTHS et al. reported that adrenochrome monosemiacarbazone 6 does not produce behavioural changes in man (37). RINKE et al. (1954) concluded that the toxic factor in "oxidised" adrenochrome was not adrenochrome, but some ill-defined further oxidation product known as "adrenochrome" and originally described by HEIMANN in 1937 (38) [cf. MARQUARDT (39)]. However, there is no evidence that adrenochrome is represented by its oxidized form. In fact, little work appears to have been carried out on the metabolism of adrenochrome monosemiacarbazone in animals or in man. Over twenty years ago FISCHER and LECOTTE reported that in man about 20-30% of the semiacarbazone is excreted unchanged, and whilst there was some evidence for conjugate formation, another 20-40% was excreted as an indole derivative which had lost its semiacarbazone moiety (40). More recently this has been reported by SIEGER et al. that in rats at a dose level of 10 mg/kg, approximately half the administered dose could be accounted for by urinary excretion within hours of administration (41). Tracer studies indicated that 85-90% of the urinary product was unchanged adrenochrome monosemiacarbazone 6. The remaining 10-15% consisted of three minor metabolites, one was not identified and the others were considered to be the sulphone ester of 5-amino-6-hydroxy-N-methylindole 7 and the azetinone indole compound 8, which retains the semiacarbazide function (SIEGER et al. (41)).
authors believed that the psychotomic agent was probably not adrenochrome, but a small quantity of a very active impurity or decomposition product of adrenochrome (44). Smythies has also referred to the possibility of adrenochrome being the actual cause of the results of attempts by Heath and Pfeuffer to obtain psychotomimetic effects from adrenochrome (33).

The most definitive studies on the psychotomimetic properties of adrenochrome in man, which have been carried out by those of Groe, Voiteckovasky, Vitter and their co-workers in Czechoslovakia. Following on from the work of Capel et al., who reported in 1960 that adrenochrome in doses of 1-2 mg evoked changes in the behavior of cats which would be expected for a psychotomimetic drug (45), Groe et al. concluded, as a result of a double-blind study, that adrenochrome, especially in higher doses, caused transitory psychotic reactions in some subjects, whilst at lower doses, neurotic and uncertain reactions were more frequently observed (46, 47). From a total of twenty-four human experiments these workers observed nine definite psychotic reactions to adrenochrome (seven from sublingual doses of 30 mg and two from sublingual doses of 15 mg) (46, 47). It was further reported by Groe et al. (1963) that both qualitatively and quantitatively different effects were obtained when they used adrenochrome synthesised by the procedure described by Feldstein (48) and when they used a commercially available preparation of adrenochrome (47). As a result of these investigations, Groe et al. concluded that the adrenochrome psychosis represents an approximate model of subtle schizophrenia-like deterioration in the area of associative thinking (47).

Groe et al. have discussed several of the factors which could possibly account for some of the confusion and contradiction in the literature concerning the psychotomimetic properties of adrenochrome (47). Different samples of adrenochrome, possibly prepared by different procedures, may be of variable purity or they may have trace quantities of other impurities present, which could lead to variable psychototoxic effects. It also appears that there is a wide range of differences in rotation to adrenochrome. The majority of the work, both chemical and psychological, that has been reported so far, has been carried out with adrenochrome prepared from 3,4-dihydroxyphenylethylamine, and in some cases, this may not have been the case, since the evidence that the sign of the rotation is altered during the oxidation procedure (8, 49), consequently adequate solutions of the usual form of adrenochrome would be desteroxytropic. The sample used by Groe et al. in their investigations was apparently prepared from dl-adrenochrome, whereas the material synthesised by Groe et al. was obtained from L-adrenochrome (47). Howser has reported that adrenochrome prepared from d-adrenochrome shows somewhat more pronounced psychological effects than that prepared from the other optical isomer of adrenochrome (9, 18).

A considerable amount of work has been carried out on the general pharmacology of adrenochrome (cf. Reviews by BACQ (5), Tatari (7), Soborob et al. (8) and psychopharmacology (Howser (9)) of adrenochrome by its possible use as a hypnotic in the salivary glands of the cat and certain other animals which brought about the in vivo oxidation of adrenochrome (50). The generally accepted involvement of the amine in adrenochrome (51) and dopachrome (derived from Dopa) as an essential intermediate in the in vivo formation of melanin pigments from tyrosine should also not be overlooked. Vander Wede and Stoerlein have described the mechanism of an enzyme system in rat brain that is capable of blocking DOPA to pigments and this same enzyme oxidizes adrenochrome (51). Vander Wede and Johnson have recently shown that serotonin is an effective inhibitor of the oxidation of adrenochrome (autoxidation) (52). These authors have further demonstrated that adrenochrome formation from adrenalin can be either accelerated or inhibited by serotonin, the nature of the reaction being dependent on the relative concentrations of the two amines (53). Inocks has also recently demonstrated the presence of a specific adrenochrome oxidase in mammalian tissues (54-56). Kalmund and Kobiljak have also shown that some animal tissues possess similar activity (57, 58).

In view of its high chemical reactivity (cf. Reviews by Howser (59) and Howser (56)) if it were not for the phenomenon of the enzyme which takes place in vivo. However, this does not entirely rule out the possible existence of adrenochrome in vivo; its concentration and the form of equilibrium in the living system. There is also the possibility of the stabilisation of adrenochrome by its potentially reversible association with other substances, e.g. a naturally occurring thiol (cf. Howser and Mattok (61), Mattok and Howser (62), Powell, Howser, Mattock and Wilson (63)).

Densow (64) and Inocks (54) have suggested that the inhibition of certain enzymes, such as acetylcholinesterase and the mammalian liver; that adrenochrome is due to interaction of these products with the SH groups in the enzyme. Krall et al. (65) have suggested that the adrenochrome inhibition of oxidative phosphorylation by rat brain mitochondria is due to the binding of free SH groups in the enzyme.

A number of workers have reported the presence of fluorescent derivatives of adrenochrome in body fluids or tissues. In no cases were the fluorescent products unambiguously identified, although they could be considered to be formed by an oxidative cyclisation of adrenochrome in the first instance. The relevant references are given in the results of Howser and Osmond (10) pp. 330 and 340.

GALZINGA has also demonstrated that a reaction occurs between acetylsaligenin and noradrenochrome (78). This reaction could be responsible for the apparent inhibition of adrenochrome by noradrenochrome. Behaviour of this type might help to explain the hallucinogenic activity of the chromes (78). Recent experiments by Galzina have suggested that certain mental illnesses may be mediated by the formation of complexes between cholinergic transmitters and catecholamine oxidation products, such as the adrenochrome (79). A considerable amount of research has been carried out during the last decade in the mechanism of amino-

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Corrélations quantitatives entre activité pharmacologique et paramètres physicochimiques.

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