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Recent Developments in Opiate Research and Their Implications for Psychiatry*

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SUMMARY. Considerable progress in opiate research has been made during the last few years regarding the identification and localization of opiate receptors in vitro and in vivo, the analysis of drug-receptor interactions and the characterization of an endogenous ligand of the opiate receptor. There is little evidence that effects induced by chronic exposure to opiates - development of tolerance and dependence - are due to changes in opiate receptor mechanisms; it is supposed that the adaptive changes occur mainly in the chain of events triggered by the drug-receptor interaction. Such changes may be directly or indirectly related to the metabolism of neurotransmitters and/or cyclic nucleotides. The obvious links between physical and psychic equivalents of opiate dependence are discussed. Present data points to the significance of brain stem and limbic structures in both these processes, monoamines probably playing an important role. Relations between psychic manifestations of opiate addiction and mental disorders are pointed out.

KEY WORDS: Opiate Receptors - Physical and Psychic Dependence - Mental Disorders.

ZUSAMMENFASSUNG. Die Opiatforschung hat bei der Identifizierung und Lokalisierung der Opiatrezeptoren in vitro und in vivo, bei der Analyse der Opiat-Rezeptor-Wechselwirkung und bei der Charakterisierung eines endogenen Liganden des Opiatrezeptors in den letzten Jahren beträchtliche Fortschritte erzielt. Es gibt wenige Hinweise dafür, daß die Wirkungen chronischer Opiatzuführung - Entwicklung von Toleranz und Abhängigkeit - durch Veränderung von Opiatrezeptormechanismen bedingt sind; es ist eher anzunehmen, daß die durch die Wechselwirkung des Opiats mit dem Rezeptor ausgelösten Mechanismen sich adaptiv verändern. Direkte oder indirekte Veränderungen im Stoffwechsel von Neurotransmittern und/oder cyclischer Nukleotide spielen hierbei eine Rolle. Die zwischen körperlichen und psychischen Äquivalenten der Opiatabhängigkeit bestehenden Zusammenhänge werden diskutiert. Die vorliegenden Daten weisen darauf hin, daß in beiden Fällen der Hirnstamm und das limbische System bedeutsam sind und wahrscheinlich Monoaminen eine wesentliche Rolle zukommt. Beziehungen zwischen psychischen Erscheinungen der Opiatabhängigkeit und geistigen Störungen werden aufgezeigt.

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SCHLÜSSELWÖRTER: Opiatrezeptoren - Körperliche und psychische Abhängigkeit - Geistige Störungen.

INTRODUCTION

Opium has been used since ancient times to suppress anxiety, emotional tension and discomfort and to induce a feeling of relaxation, contentment, well-being and happiness. Thus opium represents one of the oldest agents affecting mood. In the treatment of depressive disorders it was used long before the introduction of the modern thymoleptic drugs into therapy [9]. The euphorogenic action is the basis of psychic dependence (drug seeking behaviour) developing after repeated administration of morphine and morphine-like drugs (opiates) in medical practice, where relief from severe pain is the most important indication. Drug seeking behaviour also becomes manifest in animals and can be demonstrated in monkeys and even rodents by self-administration procedures. In parallel dependence and tolerance developes. These phenomena represent attempts of the organism to adapt to chronic opiate exposure by homeostatic mechanisms. When drug supply is interrupted, or specific opiate antagonists are administered, physical dependence becomes unmasked by the appearance of withdrawal signs, reflecting increased motor and vegetative excitability of the organism. The physical withdrawal signs are accompanied by such mental disturbances as restlessness, anxiety, depression and dispair, showing again the close association between physical and psychic manifestations of opiate action.

In view of these manifold effects it is well understandable that since the beginning of pharmacological research opiates raised much interest and morphine became a key substance of neuro-psychopharmacology. While in the past the basic mechanisms underlying opiate action remained mysterious, in spite of tremendous experimental work, considerable progress in this field has been made in the last few years. This is especially true for the first stage in the chain of events necessary for drug action, namely, the interaction of the drug with its receptor. The biochemical processes and the changes in physiological function induced by the drug-receptor interaction are still much less clear - although even in this direction some progress has recently been made.

OPIATE RECEPTOR BINDING IN VITRO

The development of opiates with high affinity to the receptors and the synthesis of radiolabelled compounds with high specific activity was essential for the identification and characterization of the opiate receptors. Thereby it became possible to study the binding of opiates in brain homogenates at dosages small enough to keep nonspecific binding low in comparison to the specific binding to the receptors. Based on a concept of Goldstein [12] exploiting the stereospecificity of opiate receptor binding a rather simple filtration technique was used by Snyder and his group [34, 46] to measure the binding of a long series of opiates to the specific receptors in brain homogenates. The big differences in potency of various opiates to displace a labelled ligand (f. e. dihydromorphine or naloxone) from the receptor reflect the differences in the affinities of the compounds to the receptor. A comparison of the affinities with the pharmacological potencies of the drugs

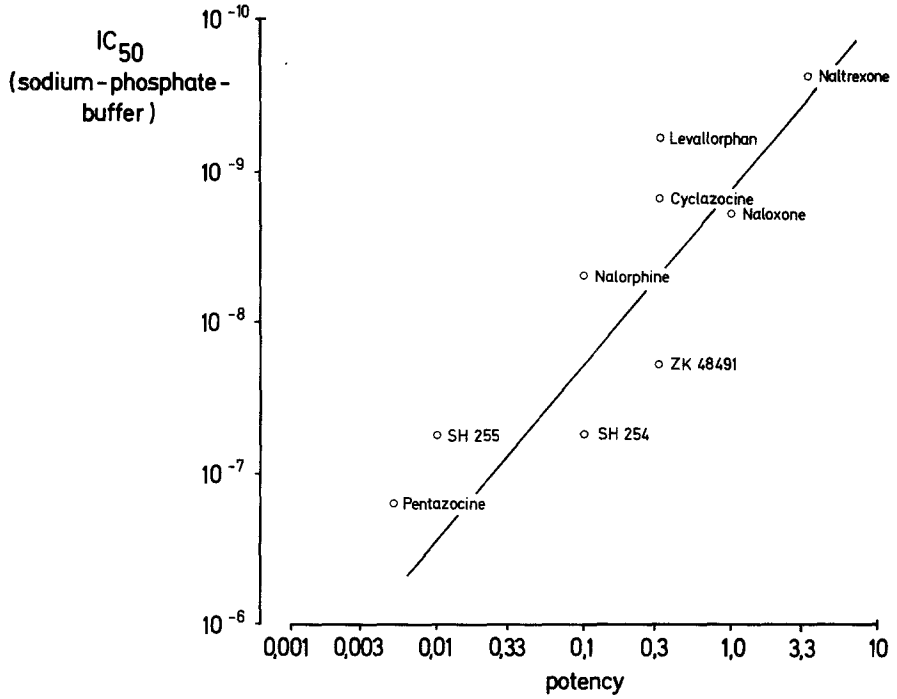

Fig. 1. Relationship between stereospecific binding in rat brain homogenates and ability of various morphine antagonists (and partial agonists) to precipitate jumping in morphine dependent rats. Ordinate: Concentration of unlabelled competitor decreasing specific binding of tritiated naloxone by 50% in sodium phosphat buffer. Abscissa: Potencies of the compounds to precipitate jumping in reference to naloxone = 1. Correlation of the regression line r = 0.86, slope 1.2. For details see Bläsig et al. [3]

revealed a close correlation between both parameters [8, 46]. A similar, close correlation between receptor affinity and pharmacological potency was also found for opiate antagonists. Fig. 1 compares the potency of a series of such antagonists to precipitate withdrawal jumping in morphine dependent rats with the stereospecific binding of these compounds to rat brain homogenates.

This close correlation between receptor affinity and pharmacological potency was an unexpected result as current theories on drug-receptor mechanisms clearly distinguish between affinity and "intrinsic activity" of a drug [2]: Drugs differ, according to this concept, in their potency to bring about the changes at the receptor initiating the pharmacological effect ("intrinsic activity") after binding to the receptor (affinity). The finding of a close parallelism between affinity and pharmacological activity raised the problem of how to explain the action of opiate antagonists, which, according to the current concept, bind to the receptor, but lack intrinsic activity. Based on the finding that sodium ions decrease the binding of agonists, while increas-

ing the binding of antagonists [35, 44] a hypothesis was developed which might help to overcome these difficulties [45]: Sodium ions induce an allosteric change of the opiate receptor; under physiological conditions (in the presence of high sodium concentrations) the receptor is present mainly in the "sodium" state, for which the antagonists show high affinity; the agonists, which have a high affinity to the "no-sodium" state of the receptor, are less effective under these conditions as only a few receptors are available which can bind them. The reversal of opiate action by the antagonists then may be explained by the assumption that occupation of the antagonist state of the receptor shifts the equilibrium towards the "sodium" state, thus reducing the number of receptors available for binding of the agonists still more. This concept can explain a series of observations and resembles models for the behaviour of the nicotinic cholinergic receptor.

This concept is also of interest in view of the partial agonists, opiates which possess agonistic as well as antagonistic properties. Binding studies performed with these compounds in sodium-free and sodium-containing media showed that, when considering these variables, the partial agonists have to be placed between pure agonists and pure antagonists and the "sodium quotient" indicates the relative preponderance of one of the two effects. Some of these partial agonists, for example pentazocine, seem to have little abuse potential in man. Thus one may speculate that there is a correlation between the sodium sensitivity of opiate binding and addictive properties of opiates [45]. The future will show, whether this aspect is helpful in developing analgesics with little or no abuse potential and whether such in vitro methods are suitable for testing it.

IN VIVO DISPLACEMENT

The synthesis of very highly labelled opiates with high receptor affinity also opened new possibilities for studying drug-receptor interactions under in vivo conditions [5] and for the correlation of such data with pharmacological effects. Though the in vitro studies showed a close correlation between the affinity of the opiates to the receptors and their pharmacological potency, the exact quantitative relationship between receptor occupation and pharmacological effect is yet to be specified. We have recently performed in vivo studies designed to help fill this gap [19]. Fig. 2 represents an experiment in which a constant dose of high labelled etorphine was injected i.v. in mice alone or together with increasing amounts of an antagonist, naltrexone. With increasing naltrexone dosage the etorphine concentration measured in brain decrease continuously and tends to plateau at about 300 µg/kg naltrexone. This indicates that an increasing displacement of etorphine from the receptors by the antagonist takes place in this dose range, while at dosages above 300 µg/kg all receptors seem to be occupied. The figure also shows the corresponding pharmacological effect: maximal analgesia, induced by the etorphine dose decreases continuously and is completely abolished at a dose of naltrexone which induces complete displacement of etorphine from the receptors.

In experiments in which the in vivo displacement of various labelled antagonists was studied, information about the relative affinities of the compounds to the receptors in vivo could be obtained. In the case of agonists, displacement was obtained by antagonists, but not by agonists. It is suggested that the pharmacologic effects of agonists interfere in some way with the dis-

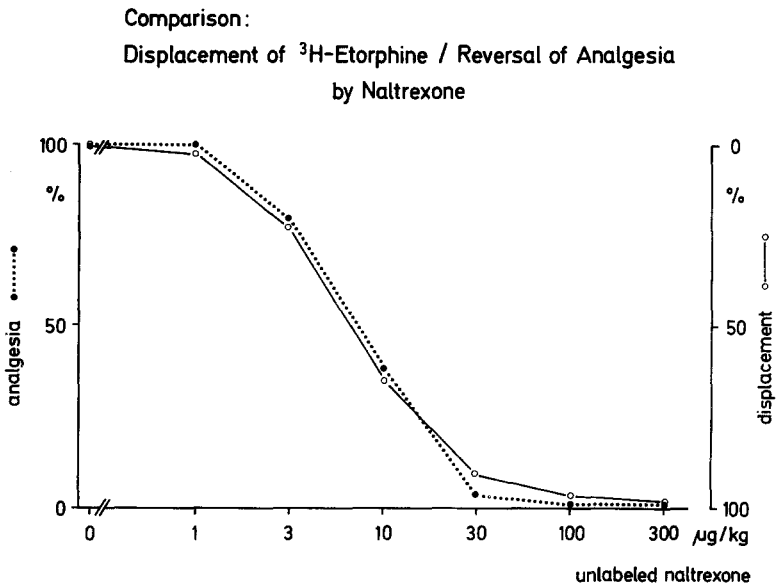

Fig. 2. In vivo displacement of ^{3}H-etorphine from the brain by unlabelled naltrexone in mice. 10 µg/kg ^{3}H-etorphine were injected i. v. either alone or together with increasing amounts of cold naltrexone and the animals killed 15 min later. In mice treated in the same way analgesia was determined at this time: Vocalization evoked by electric foot shock was used as test. The figure gives the percentage of animals showing increase in threshold for 0. 4 mnA. Each point represents mean values of at least 12 animals. (Höllt et al., unpublished results)

placement. The studies with antagonists showed a rather high correlation between the binding characteristics (number of binding sites, receptor affinity) obtained for the compounds in vivo and in vitro [19].

DISTRIBUTION OF OPIATE RECEPTORS

Studies on the stereospecific binding of opiates in homogenates of various brain areas revealed big differences from structure to structure. High densities of receptors were found, for example, in the limbic cortex, hypothalamus, striatum and midbrain, whereas the cerebellum and parts of the cerebral cortex showed only very low binding [18, 27]. A very similar receptor distribution was found in the brains of other vertebrates, including man, while in invertebrates no stereospecific binding could be detected[46]. It may be suggested that the high binding of some limbic and brain stem structures is correlated to various aspects of opiate analgesia. It is now well established that the periaquaeductal and periventricular structures of the brain stem are closely related to pain perception and to the analgesic ac-

tion of opiates [15] while the limbic structures may be of importance for the emotional aspects of these phenomena (see also later "psychic dependence").

Still more detailed information about the distribution of opiate receptors in various brain areas could be obtained recently by means of autoradiography. Such work was made possible by the use of highly labelled diprenorphine, an antagonist which, by virtue of its very high affinity to opiate receptors, shows only a minimum of unspecific binding when present in low concentrations, thus enabling the autoradiographic labelling of specific opiate binding sites, predominantly [36]. The results confirm in principle those obtained with homogenates, but give more detailed information about specific binding in particular nuclei, for example in the locus coeruleus, the pars compacta of the substantia nigra and the substantia gelatinosa of the spinal cord. Using the autoradiographic method, it was also possible to visualize the displacement of labelled opiates (etorphine) by unlabelled substance [41]. It will be a task for future work to elaborate the significance of particular binding sites and to correlate them with pharmacological effects.

ENDOGENOUS LIGANDS OF THE OPIATE RECEPTORS

The presence of highly specialized structures to which opiates bind specifically raises the question as to the physiological role of these receptive sites. While in the case of neurotransmitters or hormones the meaning of such receptive sites is quite clear, it is more difficult to understand it in the case of opiate alkaloids which are normally not present in the organism. Such considerations led various groups to look for substances in the brain which might be able to interact with opiate receptors in brain homogenates and/or which showed opiate-like actions in isolated preparations [20, 33, 49]. Recently the active principle of such extracts from brain ("enkephalin") was isolated and itentified as a mixture of two pentapeptides by Hughes et al. [21]. Interestingly, a rather high correlation between the amount of the morphine-like factor extracted from the various brain areas and the density of opiate receptors in these regions was found [45]. A polypeptide with a somewhat higher molecular weight which also binds to opiate receptors and exerts opiate actions on isolated preparations was recently detected in the pituitary gland [50, 51].

The functional significance of these naturally occurring morphine-like substances is still unknown. However, these very recent findings have given rise to stimulating hypotheses [26]. It may be suggested that these peptides exert inhibitory transmitter functions in neuronal systems mediating pain, emotions and mood [45]. In this context the action of morphine antagonists themselves (opiates not given before) has to be considered. Most data show that the pure antagonist naloxone does not display any significant pharmacological activity itself, which is difficult to explain, assuming that it competes with the endogenous ligand at the opiate receptor. However, there are a few reports showing naloxone to induce some effects when given alone [1, 22, 56]. From the fact that these effects are rather discrete it may be suggested that the role of the endogenous factors is a modulatory one which becomes manifest only under certain conditions. The physiological significance of endogenous morphine-like compounds will be

better studied when synthetic material becomes available and it may be expected that this work opens new aspects for neuro-psychopharmacology and possibly, in view of the substances contained in the pituitary gland, also for neuro-endocrinology.

MECHANISM TRIGGERED BY THE OPIATE-RECEPTOR INTERACTION

The mechanism triggered by the opiate-receptor interaction is not clear at all presently, though much data points to an interference with neurotransmitters, for example, with mechanisms involved in their release. Thus morphine has been shown to inhibit the release of noradrenaline from brain slices [30] or from the isolated mouse vas deferens and/or to reduce the output of acetylcholine from the isolated guinea-pig ileum [31]. These data seem to point to a direct action of opiates on the nerve terminals. No changes in the density of opiate receptors, however, were found after selective degeneration of cholinergic, dopaminergic, noradrenergic or serotonergic brain pathways [27] as might be expected in view of a presynaptic site of action of the opiates.

Other data points to a postsynaptic site of opiate action. Opiates applied microelectrophoretically to neurones induce a clear inhibitory effect on neu-

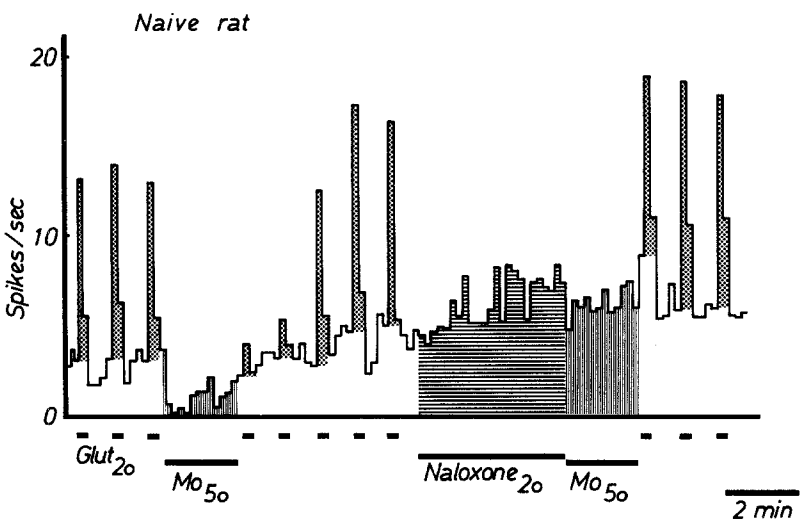

Fig. 3. Effect of microelectrophoretically applied morphine on l-glutamate-induced excitation of a cortical neurone in the frontal cortex of the rat. The numbers indicate the current applied to release the substances from the micropipette in nAmps. Glutamate pulses of 20 nA induce an about 3-fold increase of the spontaneous firing rate. Morphine blocks glutamate effects and partially the spontaneous discharge activity; the inhibition is reversed within 2-3 min after end of morphine application. Naloxone blocks both morphine effects. For details see Satoh et al. [39]

ronal discharge activity in various structures of the central nervous system; this effect fulfilled all criteria of a specific opiate action [38, 39, 58]. An interesting feature of these studies was a clear inhibitory effect of the opiates on glutamic acid-induced neuronal excitation (Fig. 3). As there is good indication that the depolarizing effects of acidic amino acids are brought about by activation of sodium influx into the neurones [59], we suggest that opiates block the chemically excitable sodium channel in the postsynaptic membrane. It might be speculated that this effect is in some way correlated to the postulated allosteric changes of the opiate receptor by sodium ions (see above). The obvious presence of pre- as well as postsynaptically located opiate receptor is reminiscent of similar findings obtained for neurotransmitter receptors; there is accumulating data showing that specific receptors for neurotransmitter are not only present in the postsynaptic membrane, but moreover, at the nerve terminals, obviously regulating transmitter release [30]. It may be expected that the elucidation of the function of the endogenous ligands of the opiate receptors will be helpful in the understanding of the mechanisms triggered by the opiate-receptor interaction.

Recent studies revealed encouraging results concerning an involvement of cyclic nucleotides in opiate action. After the first investigations of Collier [7] using rat brain homogenates, experiments in neuroblastoma hybrid cells showed strong inhibitory stereospecific opiate effects on prostaglandine E_1-induced activation of cAMP formation; this effect was correlated to the presence of opiate receptors in the various lines of neuroblastoma x glioma hybrid cells [25, 53]. Data so far obtained with other preparations are somewhat controversial, however. Further work in this field may show whether opiate effects on the adenylate cyclase system represents, as suggested by Collier [37], the decisive biochemical consequence of opiate binding of opiates to the receptor. Recently it was shown by Hamprecht's group [14] that, in contrast to the effects on cAMP, cGMP formation is greatly increased by opiates.

CHRONIC OPIATE ACTIONS

The development of physical dependence and of tolerance, both reflecting adaptive changes of the organism to chronic exposure to opiates, seem to run parallel [67]. From this it may be suggested that both phenomena are expressions of the same, still unknown mechanism. These physical equivalents of chronic opiate action are accompanied by compulsive drug taking behaviour, an expression of the development of psychic dependence on these drugs.

CHANGES AT THE RECEPTOR LEVEL

Some hypotheses try to explain the effects of chronic opiate action by changes taking place at the receptor level. In vitro binding studies, however, give no indication that either the number of the opiate receptors or the affinity of the opiates to the receptors change in a way correlated to the development of dependence [10, 19, 24]. It has to be considered, however, that changes at the receptors may be rapidly reversed during preparation for in vitro binding assay. This objection, however, does not hold for in vivo studies, in which the displacement of labelled naltrexone was studied in naive and tolerant/

dependent mice. When the amount of morphine present in the brain of chronically morphinized mice is taken into account, no significant differences in the apparent affinity and in the number of receptors between the two groups could be found [19]. This result does not support the above mentioned hypothesis, postulating that during chronic opiate treatment the equilibrium between "sodium" and "no sodium" states of the receptor shifts toward the "sodium" state.

In this context some findings have to be discussed from which changes in the sensitivity to opiate antagonists during the development of opiate dependence have been claimed, for example, Leong Way' s finding that the amount of opiate antagonists necessary to precipitate withdrawal strongly decreases with an increase in dependence [57], which is confirmed, in principle, by the findings of Takemori [54], who observed an increase in the "apparent affinity constant" for opiate antagonists during opiate treatment in mice. Moreover, recently it has been shown by radioimmunoassay that during the development of opiate dependence the efficacy of naloxone to remove morphine from the receptors in vivo increases [43]. Attempts of our group to find evidence for the development of supersensitivity to naloxone during chronic morphine treatment were less successful. No significant changes in the "apparent affinity constant" for naloxone could be found in rats and, so far, also no significant displacement of morphine in tolerant/dependent mice by naloxone using radioimmunoassay could be found [19]. A quantitative analysis of the dose-related response to naloxone revealed ambiguous results. In rats and mice a shift of the dose response curves for jumping to the left, was accompanied by an increase in the maximum effect upon increasing dependence. These characteristics seem to point more to changes beyond the receptor level than to changes occurring at the receptors themselves. In chronically morphinized rats cortical neurones responded to microelectrophoretically applied glutamic acid and acetylcholine at lower dosages than in naive rats [39]. This points to nonspecific supersensitivity and does not imply opiate receptor alterations. The loss of the inhibitory potency of microelectrophoretically applied morphine on cortical neurones in chronically morphinized rats can be interpreted in terms of tolerance development for this opiate specific effect [39]. In this context it might be speculated that these findings are associated to changes in the content or the functional state of the endogenous ligand being induced by chronic opiate treatment [26], but experimental data bearing on this question are not yet available.

CHANGES BEYOND DRUG-RECEPTOR INTERACTION

Other hypotheses try to explain chronic opiate effects by adaptive changes of the organism to opiate-induced disturbances in neurotransmitter metabolism [6, 42]. Changes in transmitter metabolism during acute opiate treatment have been observed for catecholamines, serotonin and acetylcholine. Most of these effects become largely normalized during prolonged opiate administration [16, 52]. During precipitated withdrawal the newly established homeostatic balance becomes disturbed again, resulting in metabolic changes opposite to those observed during acute treatment. In principle, rather similar results have been observed recently for opiate-induced disturbances in the metabolism of cyclic nucleotides in vitro. In a neuroblastoma hybrid cell inhibition of prostaglandine E_1 stimulated formation of cAMP by mor-

phine becomes normalized after prolonged exposure to opiates; after withdrawal of morphine a counterregulatory increase in cAMP formation takes place [25, 53]. The causal relationship between the changes in neurotransmitter metabolisms (as well as in the changes in cyclic nucleotides) and the primary processes underlying opiate action are poorly understood at present. Perhaps they represent only epiphenomena. Floyd Bloom [4] recently expressed this in the following analogy: "If we place on a pond several model boats, each representing one of the transmitters, and then throw into the pond at various times rocks representing the convulsions produced by morphine administration or withdrawal, all these little boats will naturally jiggle. They will jiggle to a degree depending on how close they are to where the rock hit the water, but none of them can really be said to have evoked the response of the pond". It has to be shown, whether the cyclic nucleotides are more closely connected to the primary processes underlying dependence than are transmitter mechanisms.

ASPECTS IN VIEW OF PSYCHIC DEPENDENCE

Psychic (psychological) dependence represents a very complex phenomenon, determined not only by the kind of the drug, but also by the personality of the drug user and by his social environment [23]. Physical and psychic dependence are not necessarily linked together, as can be seen from the fact that, in the case of amphetamine and cocaine, psychic dependence seems to occur without significant physical dependence. In the case of opiates the two phenomena greatly overlap, suggesting that their underlying basic mechanisms are closely related. Thus, any progress in the understanding of the physical manifestations of opiate action should also help in the understanding of the still more complex psychic disturbances accompanying chronic opiate intake.

Some of the most important experimental approaches to psychic dependence are self-administration techniques. The results obtained by these techniques revealed a rather good correlation between the potencies of various drugs as reinforcers in this experimental procedure and the abuse potential of these drugs in man. Experiments in which self-stimulation is induced by electrodes implanted into various brain areas, seem to be informative in this context, as it may be expected, that such brain regions (and mechanisms) where electrical stimulation has a positive reinforcing effect, may also be involved in reinforcing self-administration of drugs. By such experiments it was found that electrode locations in the limbic structures, in the extrapyramidal system and the medial forebrain bundle are the most effective in reinforcing self-stimulation [11]. It is interesting that morphine lowered thresholds for positive reinforcement when such areas were stimulated (but increased it when stimulating areas inducing negative reinforcement) [29]. There is good evidence that catecholamines play an important role in self-stimulation mechanisms, though there are some discrepancies concerning the particular role of noradrenaline and/or dopamine [11, 48]. This is interesting in view of the important role of catecholamines in the manifestation of precipitated morphine withdrawal [17]. The caudal parts of the periaqueductal grey matter and the adjacent floor of the Fossa Rhomboidea, proved to be the most sensitive sites for precipitation of withdrawal in rabbits and rats by naloxone [15, 28]. From such structures important

ascending and descending monaminergic pathways originate.

A close connection between drug seeking behaviour and withdrawal manifestation becomes obvious from the generally accepted assumption, that prevention of withdrawal represents an important component in drug-taking behaviour in addicted individuals as well as from the observation, that withdrawal signs resemble anxiety attacks [13]. In view of the well established fact that conditioning plays an important role in drug-taking behaviour, the finding that physical withdrawal signs can (depending on the particular experimental situation) either be evoked [32] or blocked [55] by conditioned stimuli is interesting and again underlines the intimate connection between the physical and psychic manifestations of opiate dependence.

Summing up all these results, there seems to be much evidence that physical and psychic equivalents of chronic opiate actions are closely linked together and that catecholaminergic mechanisms located in brain stem (especially midbrain) and limbic areas play an important role in their manifestation.

CONCLUDING REMARKS

The obviously close relationship between psychic (and physical) dependence and alterations in monoamine metabolism is highly interesting in view of the various hypotheses which try to explain endogene mental diseases by disturbances in monoaminergic brain mechanisms, for example, the amine hypothesis of affective disorders [40] and the dopamine hypothesis of schizophrenia [47]. There are impressive parallels between psychic equivalents of acute and chronic opiate action on the one side and manic/depressive disorders on the other side: Euphoria induced by acute opiate medication, anxiety and depression accompanying withdrawal. (Though there also seem to exist parallels between schizophrenia and psychic disorders occurring during opiate withdrawal, e. g. halluzinations, paranoid ideas, they are less obvious.) Of the two amines, noradrenaline and serotonin, considered by the amine hypothesis of affective disorders, noradrenaline seems to be of special interest in view of the opiate action. It should be kept in mind, however, that it is by no means clear to what extent changes at the transmitter level represent the basic disturbances or are only epiphenomena, mere consequences of still unknown basic mechanisms. The recent work on opiates seems to indicate that the basic changes underlying dependence development do not take place at the receptor level, but, instead in the "black box" of the chain of events following drug receptor interaction. Adaptive changes of enzymes involved in transmitter (and/or nucleotide) metabolism may be a part of it. In any case, there seem to exist close links between opiate actions and affective disorders. Thus it may be expected that a further elucidation of mechanisms underlying opiate actions will also help in the understanding of the disturbances inducing mental illness.

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