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The Pineal Hypothesis for Drug Dependence

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Abstract

The pineal gland constitutes a major neuroendocrine organ in the brain. By mean of its neurohormone melatonin it transduces exogenous signals such as circadian and seasonal variations of light and temperature into proper hormonal changes which adjust and adapt internal endocrine functions. Alteration of circadian rhythms has been associated with affective disorders, psychosomatic diseases and cancer.

It has been observed that light deprivation, which stimulates (the enzymes responsible for) melatonin production in the pineal, enhances the animal's ethanol preference. Similarly, administration of the pineal hormone to rats maintained under normal conditions of constant photoperiod also induced ethanol drinking.

Our hypothesis is that in normal conditions melatonin might be acting as a cerebral "pacemaker", sensitive to endogenous as well as exogenous stimuli in the attempt to maintain an equilibrate circadian interaction between the cerebral activities of endogenous aminergic and opiates systems.

Abnormal states (i.e. drug abuse) could result in altered pineal activity, then in rhythmically altered functions of cerebral opiates and/or monoamine neurotransmitters. This may led to the development of a "reward - urge for drug rhythm" resulting in craving, ending in addiction.

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Background

The pineal gland constitutes a major neuroendocrine organ in the brain. By mean of its neurohormone melatonin it transduces exogenous signals such as circadian and seasonal variations of light and temperature into proper hormonal changes which adjust and adapt internal endocrine functions. Alteration of circadian rhythms has been associated with affective disorders, psychosomatic diseases and cancer [1, 2].

It has been observed that light deprivation, which stimulates (the enzymes responsible for) melatonin production in the pineal [3, 4] enhances the animal's ethanol preference [5, 6]. Similarly, administration of the pineal hormone to rats maintained under normal conditions of constant photoperiod also induced ethanol drinking [7 – 9].

The pineal gland synthesizes serotonin and converts it to melatonin [10]. It is then possible to postulate an influence-interaction between the serotoninergic system upon pineal activities. Specifically, it has been reported that cocaine given to adult rats stimulated pineal melatonin synthesis through increased 5HT-N-acetyltransferase activity in rat pineal gland [11, 12]. Evidence for selective inhibition of median raphe neuron metabolism by treatment with melatonin and serotonin has been also described with stability of the raphe parameter in presence of noradrenaline (NA), histamine, dopamine (DA) [13, 14].

Several observations have demonstrated that the opiate system can modulate melatonin secretion from the pineal gland and that the effect of opiates may require a pineal participation. In particular, Lissoni et al. [15] reported that treatment with melatonin diminished plasma levels of Beta-endorphin in men. Acute administration of morphine resulted in a dose dependent increase in plasma melatonin concentration and this effect was blocked by pretreatment with naloxone [16]. Thus, these results seem to support the hypothesis that the opioidergic system might contribute to the activation of melatonin secretion as also proposed more recently [17, 18].

Direct involvement of melatonin within the activity of the dopaminergic system in the nucleus accumbens (nAcc) that is specifically involved in reward [19, 20] has been suggested by Gaffori et al. [21]. Their data are indeed showing a decreased locomotor activity after injection of melatonin into the nAcc of rats. This action of melatonin was completely antagonized by endorphins, and this introduces the hypothesis of a complex interaction between the DA system, the opiate system and the pineal hormone [16, 22].

In this context may also be involved data showing that treatment with gamma endorphin as well as haloperidol (DA antagonist) were followed by increased levels of melatonin [23]. Ex vivo data indicated a significant increase in brain DA and NA after treatment with melatonin [24, 25] while inhibition of the release of DA in vitro in presence of melatonin has been also reported [26, 27] and this inhibition clearly exhibited a 24-hours rhythm [28, 29].

The Pineal - Melatonin Hypothesis

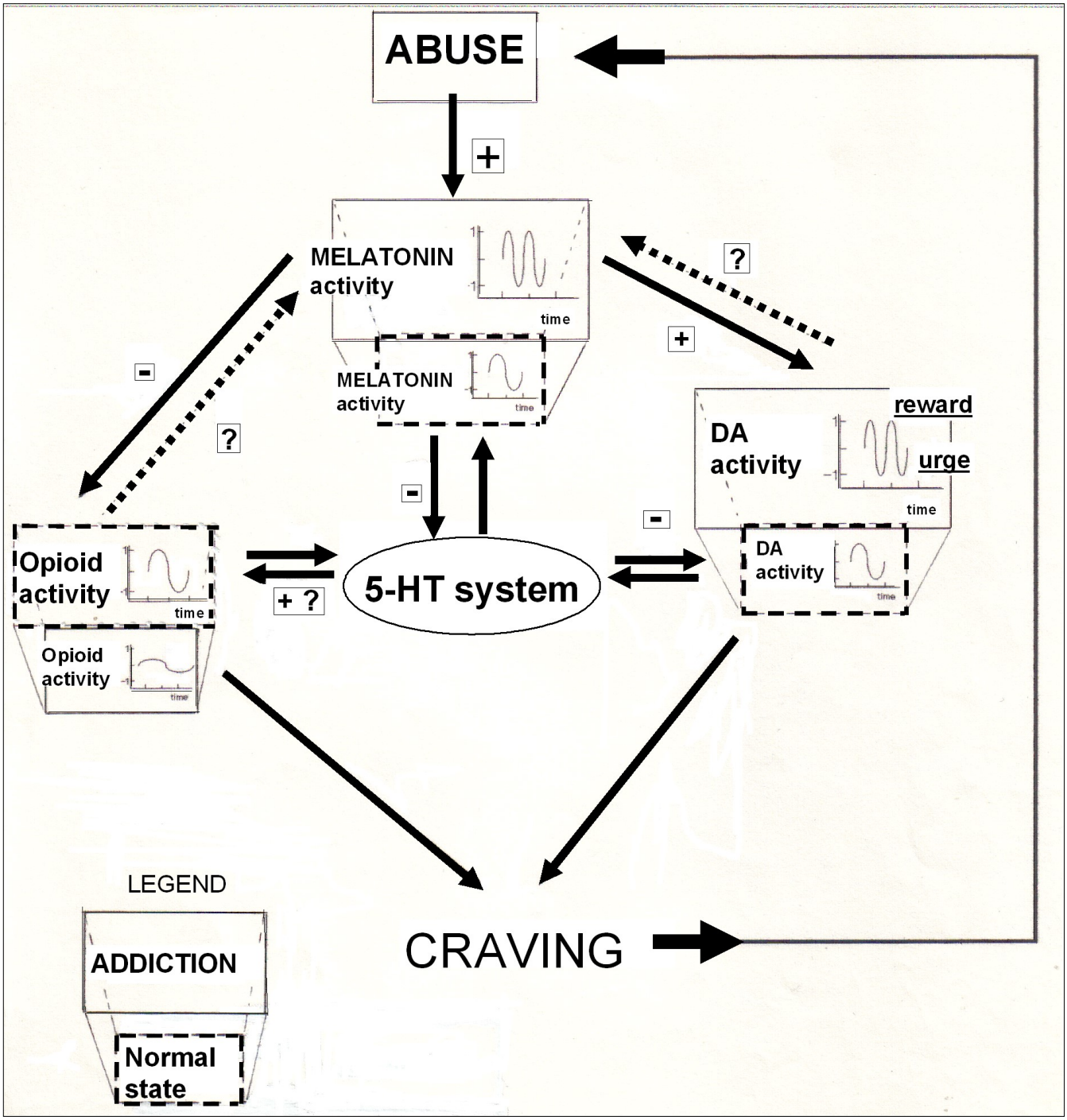
All these preliminary informations seem to indicate a close interrelationship between melatonin and the "biochemical markers" involved in the addiction - reward - craving states. This seems true for alcohol, as suggested above and by evidence that alcohol withdrawal syndrome produced a reduction of nocturnal pineal melatonin content with a concomitant elevation in pineal serotonin. In addition, a group of "abstinent" (polydrug addicted) showed remarkably higher melatonin levels than acute relapsive cases [30, 31]. It could be possible, in view of these preliminary informations, that melatonin is directly involved in the development of a state of drug addiction.

Our preliminary hypothesis could be that in conditions of drug intake, synthesis and release of melatonin in the pineal is altered (probably abnormally increased), either primarily or following alteration of the other neural systems defined above (DA, 5HT, and/or opiate). In normal conditions melatonin might be acting as a cerebral "pacemaker", sensitive to endogenous as well as exogenous stimuli in the attempt to maintain an equilibrate circadian interaction between the cerebral activities of endogenous aminergic and opiates systems (probably via a circadian mechanism). However, abnormal states (i.e. drug intake, abuse, addiction) could result in chronically altered pineal functions, resulting in rhythmically higher synthesis and release of melatonin (increased turnover). This could be either an

original effect of drug intake or subsequent to modified activity of aminergic (dopaminergic, serotonergic) and/or opioidergic systems following drug abuse [32, 33]. This change in the pineal functions could result in a rhythmically abnormal change in the functions of cerebral opiates (which should be reduced) and/or monoamine neurotransmitters, i.e. altered functions of DA in the nAcc (with a rhythmically higher increase and decrease of DA activity) and/or opposite modification of serotonergic functions, which could end in the development of a "circadian" state of reward - urge for drug (craving) resulting in addiction (see the resulting scheme 1).

Proposed Strategy to Study the Pineal - Melatonin Hypothesis

This hypothesis could be studied in models of addicted animals i.e. spontaneous alcohol drinking rats



Scheme 1. circadian state of reward - urge for drug (craving) resulting in addiction

versus spontaneous non preferring water drinking rats selected as described earlier [34] then submitted to treatment with melatonin receptor antagonists and/or agonists.

Experimental Procedures

The above mentioned compounds, as well as melatonin, will be injected (intracerebral and/or systemically) in control and addicted animals. If the "melatonin hypothesis" is correct, one would expect modification of ethanol intake in spontaneous alcohol drinking rats. Similarly, modifications should be detectable in the behaviour of addicted animals submitted to the conditioned place preference test as well as to self administration procedures (either i.v. [35, 36] or intracranial self administration of drugs [37, 38]. Modifications of neuro-biochemical parameters such as amine neurotransmitters and/or endogenous enkephalin and endorphin functions and receptor activities should be correlated to these behavioural alterations and monitored by mean of in vitro methods i.e. autoradiography [39] and in vivo techniques such as intracranial microdialysis [40] and in vivo electrochemistry [41]. In particular, previous in vitro and in vivo experiments using the electrochemical method of voltammetry [42] indicated that Melatonin is an electroactive indoleamine hormone and that it can be measurable in vivo in the pineal gland as well as in the suprachiasmatic nucleus of rat brain [43]. This, together with the possibility to concomitant voltammetric monitoring of DA and 5-HT release and metabolism [42, 44] will be a very useful tool to perform such investigation and already preliminary data have proposed a significant influence of melatonin or its antagonism on alcohol consumption in ethanol drinking rats [8]. Further data supporting the proposed hypothesis will be of help in designing new therapeutic approaches to tackle drug dependence.

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