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Brain Disintegration in Heroin Addicts: The Natural Course of the Disease and the Effects of Methadone Treatment

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Summary

The present review aims to clear up the issue of the neurological processes underlying the personality changes induced by chronic opioid use. The effects of methadone treatment on brain functions have been analyzed, too. Brain disintegration becomes evident very soon after an onset of chronic heroin abuse and continues throughout the period of drug consumption. A considerable proportion of opioid addicts are characterized by conspicuous neuropsychological deficits, which preclude the maintenance of complete opioid abstinence in this patient subgroup. At present, there are no data to testify that the effects of methadone maintenance on brain functions exceed the adverse neurological effects of chronic heroin use.

Key Words: Cognitive - EEG - Neuroimaging - Neuropsychological Aspects - Opioid

Introduction

Clinical reality shows that chronic opioid abuse induces progressive neuropsychiatric phenomena, which include acute opioid withdrawal syndrome, protracted opioid abstinence symptoms [33] and unavoidable personality changes. A range of studies has demonstrated that opioid addicts acquire antisocial and criminal life-styles after an onset of chronic heroin use, and these personality changes in opioid addicts exceed

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similar symptoms in alcoholics or cocaine addicts [7, 23, 25, 33].

Progressive personality changes in opioid addicts are a considerable burden for their families and for the community. Opioid addiction is associated with a high risk of death. Only about 50% of these patients live longer than 20 years after an onset of opioid use [6], and about 10% of them try to commit suicide over a 12-month period [11]. It is also appropriate to stress the contribution of heroin addiction to the prevalence of HIV infection and other morbid conditions. Hence, the progressive personality changes seen in opioid addicts represent the core and most serious complication of chronic opioid use. Unfortunately, all existing treatment approaches, including complete opioid abstinence, do no more than partly alleviate these personality changes in a proportion of addicts.

The present review aims to clear up the issue of neurological processes underlying the personality changes induced by chronic opioid use. The effects of methadone treatment on brain functions in this patient population have been analyzed, too.

Progressive brain disintegration in heroin abusers

Abnormal electric activity in central brain regions in heroin addicts.

There is growing evidence that electric activity in central brain regions is radically altered in heroin addicts, and that these alterations emerge very soon after an onset of chronic opioid use. In the late '90s heroin addiction spread all over Russia on the scale of an epidemic. In that period, street heroin was relatively pure and in most cases it did not contain contaminants. The duration of daily heroin use ranged from several months to 3.5 years in the addict population of Moscow. Besides this, a considerable proportion of Russian heroin abusers were very young (mean age about 23 years) and otherwise psychiatrically healthy people coming from well-educated and socially integrated families. This gave us the opportunity to evaluate the early effects of daily heroin use on the electric activity of the brain in young patients with a relatively normal psychiatric premorbid history.

We found that the mean frequency of alpha2 band electric activity in heroin addicts was significantly above normal throuhout the brain, as assessed by comparison with controls, and that this electroencephalographic (EEG) phenomenon was significantly correlated with the duration of chronic heroin use in our patient cohort [34]. The most important finding in this study referred to relationships between changes in brain electric activity and selective cognitive dysfunctions in the early stages of heroin addiction. Planning deficits (the Tower of London test) was strongly associated with alpha2 mean frequency increases in central derivations (C3, Cz and C4) in our patients [13]. This association was mediated by the length of chronic heroin use in the right hemisphere (C4), whereas it was not related to chronic heroin use at the left central lead (C3). These data gave grounds for hypothesizing that the functioning of central brain structures is affected very soon after an onset of chronic heroin use, and that these alterations first arise in the left hemisphere and a little later spread to the central region of the right

hemisphere in heroin addicts. At least four other research groups similarly recorded-electric activity abnormalities in central brain regions in patients with a mean duration of chronic heroin use ranging from 3.5 to 15 years; all of these findings refer to slow wave activity in central structures.

Shufman and colleagues [39] reported an excessive intensity of delta activity at Cz in abstinent patients with a mean length of chronic heroin use of 3.5 years, but in no case did these authors find any similar electric abnormality in current heroin users with a mean duration of opioid use of 4.5 years. Papageorgiou and colleagues [31] also found an abnormal spread of slow wave electric signals from C3 to right hemisphere central and frontal regions during the performance of a cognitive test by heroin addicts who had been abstinent for at least 6 months. The most important findings on electric activity in central brain structures in heroin addicts were reported by Franken and colleagues [16, 17]. This research group found that heroin cues elicited slow wave-evoked potentials with the largest amplitude at central leads (C3, Cz and C4) in heroin addicts who were compared with normal controls, and that the amplitude of these potentials was significantly correlated with the severity of craving for heroin. These authors also reported a significant correlation between craving severity and the coherence of delta activity at central temporal derivations in the same patient cohort.

It should be noted that in our patient cohort we recorded significant correlation between the intensity of delta activity at Cz and C4 and the amounts of heroin which patients used per day before their admission to the in-hospital unit. Following a different line of inquiry, Greenwald & Roehrs [20] found increased delta activity in central derivations in addicts who self-administered fentanil, in comparison with patients who received the drug passively. Both findings may be interpreted as an indirect confirmation of causal association between delta activity in central brain structures and craving processes.

These contemporary EEG studies go to show that central brain structures are radically altered in heroin addicts at an early stage. This functional brain system is involved in incentive sensitization and craving processes, and is unable to adequately support cognitive operations which do not relate to heroin use in this patient population. The severity of the dysfunction of central brain structures seems to be directly related to the severity of addiction behavior.

All the characteristics of the central brain electric system mentioned above closely resemble the abnormalities of the mesocorticolimbic dopamine system in opioid-abusing subjects. Animal and human studies have shown that the structures of mesocorticolimbic system (dopamine neurons of the ventral tegmental area, the nucleus accumbens and anterior cingulate gyrus) are highly sensitized to opioids and neuroplastically altered in addicts [35, 36]. The baseline activity in these structures is abnormal in abstinent heroin abusers [18]. These structures are involved in incentive sensitization and craving processes [8, 9, 38], and are unable to adequately support cognitive operations which are not related to drug addiction behavior in opioid addicts [14, 15, 26]. Hence, EEG studies confirm the findings of human neuroimaging and animal experimental studies on the quickly initi-

ated, inevitable long-term reorganization of the dopamine mesocorticolimbic system in heroin abusers.

Frontal dysfunction in heroin addicts.

In our study of heroin abusers, a subgroup of patients with a duration of chronic heroin use of under 18 months did not differ from healthy controls in their performance on two cognitive tests evaluating prefrontal functions (Delayed Alternation Test and Wisconsin Card Sorting Test) [4]. Even so, individual variations in cognitive performance were significantly associated with the amount of heroin which patients self-administered each day before their admission to the in-patient unit [5]. Patients who performed poorly on both prefrontal tests self-administered about 0.7 gram of heroin per day, whereas patients who performed 'ideally' on prefrontal tests used only 0.18 gram per day. The subgroup of patients with a selective deficit on Delayed Alteration Test self-administered 0.4 gram per day. Three subgroups did not differ in the duration of chronic heroin use. We concluded that premorbid prefrontal dysfunctions significantly affect patterns of daily heroin use in subjects with a relatively short drug use history.

Four other research groups reported significant clinical effects of prefrontal dysfunctions in opioid addicts. Gerra and colleagues [19] observed right prefrontal hypoactivation in heroin addicts with antisocial and/or depressive personality characteristics, i.e. a subgroup of patients with especially severe addictive behavior. Similar findings were reported by Bauer [3], who found significant correlation between childhood conduct disorder and amplitude of the P300 component of EEG evoked potential which was recorded during a continuous performance test in adult drug-abusing patients. Besides this, Pezawas and colleagues [32] observed a significant effect of the frontal lobe volume on the longest periods of abstinence in methadone-maintained patients, and Lyvers & Yakimoff [29] found a correlation between the severity of opioid dependence and the number of perseverative errors made in performing the Wisconsin Card Sorting Test in their similar patient cohort. Hence, prefrontal dysfunction is an individual characteristic of heroin abusers, and it underlies the prominent severity of drug abuse patterns in a proportion of opioid addicts.

Although patients with a short duration of chronic heroin did not differ from normal controls on their performance on the Delayed Alternation Test in our study, patients with a longer heroin abuse history (18 months to 3.5 years) gave a significantly poorer performance on this orbito-frontal neuropsychological task compared with normal subjects ($p=.04$). Moreover, we found a significant association between performance on Tower of London test (medial prefrontal cortex) and the duration of chronic heroin use [4]. These data gave grounds for concluding that dysfunctions in the orbito-frontal and medial frontal cortex progress in subjects sowing a chronic use of heroin.

Two other research groups reported a similar association between frontal cortex deficits and chronic opioid use history. Liu and colleagues [27] found significant and negative correlation between bilateral white matter volume and length of chronic heroin usage in addicts with a drug abuse history of 2 - 15 years. Franken and colleagues [17] reported significant negative correlation between frontal interhemispheric coherence and

chronic heroin history duration. It should be noted that, along with neuropsychological deficits, brain electric activity in frontal regions was also significantly correlated with heroin abuse history in our patient cohort [34]. Overall, these findings provide evidence that prefrontal dysfunction progresses in opioid users during their period of drug consumption.

Concomitant brain damage in opioid addicts.

Concomitant brain damage is common in opioid addicts. About 70% of opioid users report non-fatal overdoses and mild to moderate head injuries, which significantly affect cognitive performance in this patient population [10]. Concomitant alcohol and cocaine abuse also significantly contribute to brain damage in chronic opioid users [10, 28].

Ischaemic-hypoxic brain lesions are commonly found in long-term heroin addicts, and these brain alterations develop at significantly earlier age than in non-drug abusing controls [1, 28]. Concomitant adverse factors probably underlie the posterior brain disintegration which was reported in addicts with a long-term heroin history (about 15 - 20 years), but not in patients with a shorter duration of chronic heroin use [2].

The course of brain disintegration in chronic heroin users.

The findings of neuroimaging, EEG and neuropsychological studies cited above may be summarized as follows. Brain disintegration becomes apparent very soon after an onset of chronic heroin abuse. First, opioids inevitably reorganize the dopamine mesocorticolimbic system, which begins to implement addictive behaviour and is ineffective in other domains in chronic heroin users. Second, prefrontal dysfunction progresses in opioid addicts, and its severity is associated with especially prominent patterns of addictive behaviour. Third, concomitant brain damage is another common feature in heroin addicts, and may contribute to cognitive dysfunctions in this patient population.

Effects of methadone treatment and complete opioid abstinence on brain functions

In the second part of this review we make an attempt to summarize the findings of neurological and neuropsychological studies which have compared methadone-maintained patients with completely abstinent former heroin addicts. Few studies have addressed this issue, but we were able to identify six of them.

Physiological correlates of complete opioid abstinence.

Gritz and colleagues [21] registered significant elevation of heart rate with the same trend for arterial blood pressure in opioid addicts who had been completely abstinent for two months. At the same time methadone-maintained patients demonstrated normal haemodynamics, along with a somewhat depressed respiration rate. This study therefore confirmed clinical observations concerning persistent sympathetic hyperactivation in abstinent opioid addicts [33], whereas methadone treatment normalized autonomic

dysfunctions in this patient cohort.

Kouri and colleagues [24] studied cognitive evoked potentials in addicts using heroin and cocaine. On admission day, patients did not differ from normal controls in the EEG parameters that were evaluated, whereas on the 12th day of heroin abstinence two subgroups of patients demonstrated a significant decrease in P300 compared with healthy controls. On the 14th day of treatment, the buprenorphine group showed complete normalization of the EEG-evoked potential, whereas the placebo group still was characterized by a significant decrement in the P300 amplitude.

The two studies just cited provided evidence that complete opioid abstinence is a state in which discomfort is experienced in association with sympathetic hyperactivation and non-specific cognitive dysfunctions. It is obvious from clinical practice that only a proportion of addicts are able to overcome these symptoms of protracted opioid withdrawal and maintain stable sobriety.

EEG and neuropsychological deficits in abstinent and methadone-maintained addicts.

Shufman and colleagues [39] demonstrated that both abstinent and methadone-maintained patients were characterized by abnormalities in brain electric activity not found in healthy controls. The two groups demonstrated similar significant deficits of alpha2 band power, but differed in delta and alpha1 power displayed. Delta activity was significantly higher in abstinent subjects, whereas the intensity of alpha1 activity was higher in methadone-maintained patients. Similar data were reported by Gritz and colleagues [21], who recorded significant slower alpha rhythms in methadone-maintained patients than in normal controls, with intermediate alpha peak frequencies in abstinent subjects.

Cognitive dysfunctiona are also commonly reported in both methadone-maintained and abstinent patient populations. Two neuropsychological studies found cognitive deficits to be more frequent and more conspicuous in methadone-maintained patients than in abstinent addicts [12,21]. However, methadone-maintained subjects were characterized by considerably longer histories of street opioid use compared with abstinent controls in both reports. Bauer [2] too observed significantly more radical changes in visually evoked potentials in methadone-maintained subgroups compared with abstinent ones. Even so, statistical procedures showed that these differences were mediated by the length of chronic heroin use, but not by the effects of methadone treatment.

Methadone-maintained patients and abstinent former addicts with an equal length of chronic heroin use were compared in the study of Mintzer and colleagues [30]. Psychomotor speed was slower in both patient groups than in normal controls, while this deficit was even more marked in former addicts than in the methadone group. However, methadone-maintained patients demonstrated additional cognitive impairment while performing the Gambling Task, which measures orbito-frontal cortex functions. In our opinion, these data provided evidence that the orbito-frontal dysfunction underlies the inability of methadone patients to maintain complete opioid abstinence, whereas addicts showing a normal orbito-frontal performance entered the abstinent subgroup.

Overall, the studies just cited can be summarized as follows. Both methadone-maintained and abstinent addicts display cognitive impairment when compared with healthy controls. At the same time, patients entering methadone maintenance treatment are characterized by more comspicuous cognitive deficits than patients who are able to maintain complete opioid abstinence.

Correlates of cognitive dysfunction in methadone-maintained patients.

At least 4 neuropsychological studies failed to find any significant association between methadone dosage regimen and cognitive performance [10, 21, 37, 40]. Moreover, Gruber and colleagues [22] demonstrated an improvement in cognitive functions as little as two months after the beginning of methadone treatment in opioid addicts. At the same time, cognitive deficits in methadone-maintained patients was significantly correlated with the number of non-fatal overdoses, mild to moderate head injuries, severity of alcohol dependency and global health in the study of Darke and colleagues [10]. These data all provide evidence that methadone maintenance per se does not seem to radically affect cognitive functions in chronic opioid abusers. However, mildly sedative effects attributable to methadone may not be completely excluded by the data just quoted.

Conclusion

From the neurological point of view, populations of opioid addicts are not homogeneous. A considerable proportion of opioid addicts are characterized by conspicuous neuropsychological deficits, which preclude the continuation of complete opioid abstinence by this patient subgroup. So far, no data have been found to testify that the effects of methadone maintenance on brain functions exceed the adverse neurological effects of chronic heroin use.

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