

Maternal Separation and the Risk of Drug Abuse in Later Life

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Review Article

Abstract

Maternal separation (MS) is defined as the termination of the continuity of mother-child relationship after the relationship is established. Although MS and maternal deprivation are different in terms of their definitions, these two terms are usually used interchangeably. This review aims to investigate the effect of MS on drug intake in adulthood. It has been proved that animal models are helpful in evaluating the effects of MS on drug intake risk in adulthood. There are relatively acceptable studies in this field on some drugs such as morphine, ethanol, and cocaine. However, very few animal studies, or even no animal study, have been conducted on some other drugs. The majority of these studies have considered MS as a risk factor for drug intake in adulthood. Different mechanisms are proposed for this phenomenon. Brain reward pathways are one of the main exploratory pathways of this process. Despite the importance of the issue, no human study with a specific concentration on investigating the relationship between MS and drug abuse in later life was found. Causal studies are warranted on humans to investigate the effect of MS on drug intake in later life.

Keywords: Early life stress; Maternal deprivation; Addiction

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Introduction

Brain function is under the influence of environmental factors, signals, stimuli, and acquisitive events throughout the entire lifespan. Events occurring during the critical growth periods such as neonatal period can have lasting effects extending to adulthood. Stress is an obvious experience of early years after birth. According to studies, stressful events experienced during the early years of life can have negative effects on behavioral and physiological functions such as growth, metabolism, and inflammatory and immune responses later in life. Proliferation, differentiation, and neuronal migration will grow during the 1st weeks after birth. Hippocampal granule cell neurogenesis in rodents and humans reaches its peak in the 2nd week of life and the 2nd month after birth, respectively.¹

Maternal separation (MS) is a stressful factor in early childhood occurring at different time intervals after birth, especially during infancy.² As an unpleasant experience of early life, MS causes cognitive, emotional, and neurochemical disorders in adolescent rats.³ Affecting the hypothalamus-pituitary-adrenal axis, the termination of the usual mother-child relationship cause lasting changes in emotional responses and physiological and neurobiological functions during puberty.⁴

Since a large number of children were deprived of their mothers after World War II, MS and its effects on children were vigorously addressed in the World Health Organization (WHO) report.⁵ According to Bowlby⁵ in this report, "the infant and young child should experience a warm, intimate, and continuous relationship with his mother (or permanent mother substitute) in which both find satisfaction and enjoyment."

According to studies, MS leads to some behavioral and neurochemical disorders such as abnormal emotion-related behaviors, spatial memory loss, increased locomotor activity and disrupted dopaminergic, and serotonergic activity. Morphological changes following MS have been also reported.^{3,6} These observations show that MS can cause lasting changes in brain plasticity and it causes changes in the growth of the areas involved in the stressful stimuli.⁶

There are plenty of evidence indicating the

relationship between early life MS and increased drug abuse in adults. In a study by Ploj et al.,⁷ it was found that MS for 360 minutes 1-21 days after birth results in lasting changes in the concentration of dopamine receptors in brain and increased intake of ethanol in adult male rats. Another study showed that MS for 1 hour 2-9 days after birth could lead to increased cocaine self-administration in adult male rats.⁸ A study by Vazquez et al.² showed that MS for 3 hours 1-14 days after birth is considered a risk factor for morphine dependency in adult male rats.

The present study aims to provide scientific evidence for the relationship between MS and substance use disorders based on a narrative review.

Definitions of MS and maternal deprivation (MD)

In related literature, there is generally no difference between MS and MD, and they are used interchangeably.⁹ MS is defined as a break in the continuity of the relationship after the mother-child relationship is established.⁹ Regarding the definition of deprivation, Gandelman¹⁰ distinguished between privation and deprivation. Privation addresses the cases in which the offspring has not seen his/her mother since birth while deprivation occurs when the offspring experiences being with his/her mother and attachment, but this attachment is terminated temporarily or permanently for some reasons.¹⁰

Animal models (rodents) use the two "MS" and "early deprivation (ED)" terms.¹¹ MS refers to daily separation from the dam so that the animal lives next to the littermates. In ED, however, the animal is separated from both its mother and littermates (social isolation).¹¹

In a study on 3712 middle-aged individuals, Kumari et al.¹² divided MS into the following six groups: mother die, mother ill, adoption, divorce/separation, evacuation, and other. While evaluating the effect of MS on the child's physical, mental, and social health, it should be noted that every child has his/her own unique history with a different vulnerability. While a person may live in a peaceful stress-free environment after MS, a child may experience hard times in an orphanage. On the other hand, merely being with mother would not be sufficient and experiencing maternal abuse and neglect phenomena are harmful to the child's health by themselves.¹³

Moreover, it should be noted that the effects of MS can be associated with the child's age, the length of separation, type of separation, and gender.¹⁴

The effects of MS on children may have different physical, mental and social aspects. Since depriving people of their mothers is unethical, experimental studies are focused on animal models such as mice, rat and rhesus monkeys and so on.¹⁵ Studies on humans with the purpose of discovering the relationship between MS and substance use disorders are usually retrospective in nature.^{16,17}

In this study, MS and MD have been considered equivalent to each other, and Yarrow's⁹ original definition, which is apparently more comprehensive, will be considered; that is, the continuity of mother-child relationship is broken for some reason.

History

There are many comments made by psychologists like Freud about the adverse consequences of MS on children.⁵ On the other hand, the WHO report on the adverse effects of MS backs to more than 6 decades ago.⁵ Despite the mentioned facts, studies on the negative effects of MS on children's physical, mental, and social health are still in its infancy stage. In his report, Bowlby⁵ emphasized that children's health will sustain a loss if such condition is not met. It seems that the sensitivity of the scientific community in those years was rooted in the deprivation of a large number of European children due to World War II so that in a review article in the pediatrics in 1956, negative consequences of MS on children's health were explained.¹⁸ Since those years on, the vast majority of the studies have been conducted in animal environments. More than 700 papers related to MS have been indexed in PubMed since 1966, of which < 10% have investigated the relation of drug abuse with MS.

In the 20th century, scientists mostly considered MS as a vulnerability factor role for children's problems in adulthood. Since the start of the 21st century, however, studies have considered the role of MS as a roughly direct cause for children's health problems¹⁹ so that not only these effects sustain until adulthood, but also they are extended to the next generations.²⁰

Animal studies on the relationship between MS and drug abuse

Animal studies on this issue are mostly conducted on rats. During MS process, litters are separated from dams for 15 minutes to 6 hours for 2 weeks on daily basis.²¹ It has been well established that these brief separations can result in longstanding changes in brain function which, in turn, leads to neurochemical and behavioral changes in adulthood.²² Studies have been conducted on different materials, and the studied model has often been self-administration and partly oral consumption.²¹⁻²⁵ It has been well-documented that to a large extent, these models are predictive of drug abuse vulnerability in humans.²⁵

MS and opioids abuse

In a study, littermates were separated from their mother for 14 days and 3 hours/day. Researchers found that MD causes basal hypoactivity of the enkephalinergic system and hypersensitivity to the reinforcing properties of morphine. Therefore, MS was identified as a risk factor for morphine dependency in adult rats.²

In another study, the effect of MS on oral self-administration behavior in rats was evaluated in terms of amphetamine, ethanol, morphine, and cocaine.²⁴ The greatest impact of MS on oral drug consumption was seen regarding morphine and amphetamine, respectively.²⁴ Other animal experiments also found similar results.²⁶

MS and ethanol abuse

The main part of studies on the effect of MS on ethanol intake in rats or mice have concluded that MD is a risk factor for alcohol consumption during adolescence and adulthood in males²⁷ though this relationship is not observed in females.^{28,29}

Daoura et al.³⁰ deprived Wistar rat pups of their mother for 15-360 minutes during the first 20 days after birth on daily basis. After adulthood, ethanol consumption was considerably higher in rats with 6 hours deprivation of their mothers per day compared with those with 15 minutes deprivation per day. Adolescent rats had greater consumption than adult ones. In a recent study, Wistar rats that were deprived of their mother during post-natal days were exposed to the two-bottle free choice paradigm. The study showed

that although there was no difference in baseline voluntary alcohol intake between the deprived and the control groups, after stress exposure, the deprived rats consumed remarkably greater ethanol than the control group.³¹

Neurochemical changes in brain serotonin systems,^{32,33} changes in the endocannabinoid system (ECS),³⁴ and changes in the function of hypothalamus pituitary axis³⁵ are introduced as some probable mechanisms.

MS and cocaine abuse

The relation between cocaine consumption in adult rats and neonatal isolation has been well demonstrated. In neonatal isolation, pups are separated from both dam and littermates. Accordingly, this deprivation is more severe than MS case. Neonatal isolation leads to the maintenance of cocaine self-administration enhanced acquisition in rats.^{8,36} Kikusui et al.³⁷ showed that MS can enhance sensitization to cocaine in mice. In this experiment, litters were separated from their mother for 1 hour during the 1st-13th post-natal day on daily basis. The mice with MS experience showed significantly greater sensitized hyperactivity against cocaine challenge test compared with the control group.³⁸ Martini and Valverde showed that a single episode of early MS can alter reward function and lead to impairment in the motivation for cocaine self-administration in adolescent mice.³⁸

MS and cannabinoids abuse

It has been well accepted that MS causes alteration in ECS.³⁹ According to Marco et al.⁴⁰ a single 24 hour MS episode during early neonatal life in mice might trigger impulsive behavior and depressive trait. These psychological traits can increase the risk of cannabinoids abuse among adolescents if they are exposed to them. Animal studies have not directly investigated the role of MS in raising the risk of cannabinoids abuse, as observed in opioids and alcohol. However, research suggests that a person with MS experience is more susceptible to sex-specific neurodevelopmental mental illnesses if exposed to cannabinoids.^{41,42}

MS and methamphetamine (Meth) abuse

The only study on this issue was conducted by Lewis et al.⁴³ In a study, Long-Evans pups were

separated from their mother for 15 or 180 minutes, on daily basis, during the first 2-14 days of their lives. In the group experienced separation for 180 minutes, a strong increase in Meth self-administration was seen. Lewis et al.⁴³ concluded that MS may contribute to liability toward Meth intake.

MS and nicotine abuse

The extensive literature review found no animal study on the role of MS in the vulnerability of laboratory animals to tobacco consumption.

Human studies on the relation between MS and drug abuse

There are only very few studies on this issue. The reason may be traced in the following three reasons: First, conducting experimental studies on humans and exposing humans to the considered risk factor (MS) is not possible as it disagrees with the principles of research ethics. Second, the scientific literature of animal studies, compared to other addiction research fields, is not so rich to provide considerable information for human studies. Finally, it is not a long time that the attention of researchers has been attracted to the importance of the 1st day of life (the first 1000 days of life).⁴⁴ The first 1000 days of life which includes 270 days of intrauterine life and the first 2 years after birth have a significant effect on individuals' behavioral and physical development and their health in later life.⁴⁵ In general, it can be argued that scientific research on the effect of MS on vulnerability toward drug abuse is still in infancy stage, and the issue has not been addressed in human studies to the extent of our expectations. Most of the studies have only investigated the effect of these critical periods on physical health.⁴⁴⁻⁴⁶

Reward deficiency syndrome is one of the mechanisms discussed in explaining the importance of early days of life as background risk factors for addiction in adolescents and adults.⁴⁷ In other words, since individuals with low levels of D2 receptors do not capture feelings of reward and pleasure through ordinary activities, they engage in alternative behaviors such as drug abuse and pathological gambling. This syndrome is caused by impairment in reward pathway of the brain. It has been well established that MS is one of the environmental

stressors that is the cause of disturbance in dopaminergic system and change in mesolimbic dopamine system of the brain.⁴⁸⁻⁵⁰

The vast majority of studies investigating the effect of MS on mental disorders have been conducted on diseases such as anxiety and depression,¹² personality disorders,⁵¹ and behavioral problems⁵² and no exclusive human study, whether retrospective or prospective, was found regarding the relationship of MS and drug abuse in humans. Only one study on the effect of early weaning concluded that the chance of weaning in childhood (before 1 month of life) was greater in individuals hospitalized in a psychiatric ward with an alcohol-related diagnosis.⁵³ Most of the studies in human environments have evaluated the relation between drug abuse and child abuse and neglect,^{13,17,54} all of which were indicative of a strong relation.

Conclusion

It may be concluded that due to changes in the midbrain, especially decreased activity of the mesolimbic system, as well as the creation of reward deficiency syndrome, MS leads to a group of medical signs and symptoms that collectively indicate or characterize an abnormal condition named "MS syndrome." Although animal models are to a great extent informative in finding the adverse effects of MS on drug abuse in adolescents and adults, further causal research is required to be conducted in human environments by considering research ethics.

Conflict of Interests

The Authors have no conflict of interest.

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محرومیت از مادر و خطر سوء مصرف مواد در زندگی آینده

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مقاله مروری

چکیده

جدایی از مادر (Maternal separation یا MS) تحت عنوان قطع استمرار ارتباط بین مادر و کودک بعد از استقرار این ارتباط تعریف می‌شود. اگرچه تفاوت‌هایی در تعریف MS و محرومیت از مادر وجود دارد، اما در اغلب موارد این دو واژه به جای هم به کار می‌روند. مطالعه مروری حاضر به بررسی تأثیر MS بر مصرف مواد در سنین بزرگسالی پرداخت. ثابت شده است که مدل‌های حیوانی برای ارزیابی اثرات MS بر خطر مصرف مواد در بلوغ مفید می‌باشند و مطالعات قابل قبولی در این زمینه در خصوص برخی موارد از جمله مورفین، اتانول و کوکائین انجام شده است، اما مطالعات در مورد برخی مواد بسیار اندک می‌باشد و یا هیچ مطالعه حیوانی انجام نگرفته است. بیشتر پژوهش‌ها، MS را به عنوان عامل خطری برای مصرف مواد در بزرگسالی مطرح نموده‌اند. مکانیزم‌های متفاوتی برای این پدیده مطرح شده است که از عمده‌ترین مسیرهای بیانگر این فرایند، مسیر پاداش مغز می‌باشد. با وجود اهمیت موضوع، مطالعه انسانی که به طور اختصاصی به بررسی ارتباط MS و مصرف مواد در سنین بالاتر پرداخته باشد، یافت نشد. انجام مطالعات سبب‌شناختی بر روی انسان‌ها به منظور تعیین تأثیر MS بر مصرف مواد در سنین بالاتر ضروری به نظر می‌رسد.

واژگان کلیدی: استرس اوان زندگی، محرومیت از مادر، اعتیاد

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