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Commentary

Maternal separation alters drug intake patterns in adulthood in rats

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ABSTRACT

Maternal separation/handling (MS/H) is an animal model of early life stress that causes profound neurochemical and behavioral alterations in pups that persist into adulthood. Many recent studies have used the MS/H model to study changes in drug effects in adulthood that are linked to behavioral treatments and stressors in the perinatal period. The drug effects focused on in this review are the reinforcing properties of the abused drugs, cocaine and alcohol. A striking finding is that variations in maternal separation and handling cause changes in ethanol and cocaine self-administration. Further, these changes indicate that various manipulations in the perinatal period can have long lasting effects of interest to biochemical pharmacologists. This article will review recent studies on ethanol and cocaine self-administration using the MS/H model and the neurochemical alterations that may play a role in the effects of MS/H on ethanol and cocaine self-administration. Studying the MS/H model can provide important clues into the vulnerability to drug abuse and perhaps identify a crucial window of opportunity for therapeutic intervention.

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1. Introduction

From the point of view of a pharmacologist, a number of treatments and manipulations are known to alter the effects of various drugs. For example, repeated administration of some centrally acting drugs such as psychostimulants can result in tolerance or sensitization depending on how the drugs are administered. This article describes changes in cocaine and alcohol self-administration in rats, that seem to last a lifetime, after treatments and stressors during the perinatal period. Drug self-administration in animals is a robust procedure that is highly predictive of drug abuse liability in humans [1–3].

In general, maternal deprivation, social stress, neglect and physical and sexual abuse in early life have been linked to behavioral disorders in humans and in animals [4–10]. These disorders include depression, anxiety, drug abuse [11–14], altered reproductive behavior [15] and compromised learning [16,17]. Many studies have shown that early perinatal procedures in rats can permanently alter various patterns of drug use and behavior in adulthood [18–23]. Maternal separation (MS) is one of these procedures and the focus of this review. MS involves the daily separation (15 min to 6 h) of litters from the dams during the first 2 weeks of life. These brief separations cause profound neurochemical and behavioral changes in the

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pups that are found in adulthood. This review is focused on how the changes induced by MS affect behaviors associated with drugs of abuse. While it is generally recognized that early development is a time of vulnerability, this mechanism of altering the effects of drugs in adulthood is relatively unknown and underappreciated.

2. Procedures of maternal separation and handling (MS/H)

Models of early life stress, such as MS, use perinatal manipulations where the length of separation and handling sometime varies from laboratory to laboratory. Table 1 describes the MS procedure used by our laboratory and some others. Rats that are separated for fifteen minute per day (MS15) during the first two weeks of life have been used in many studies and are sometimes referred to as producing ''handled'' rats. This group shows less stress reactivity than animals separated for 180 min per day (MS180) which are commonly referred to as ''maternally separated'' [16,21]. Other laboratories have used up to 6 h of separation (MS360) [24–27]. In each experiment, one animal, or sometimes two, is taken from a different litter of the same treatment group to minimize possible litter effects. Treatments usually extend into the second postnatal week because of the suggestion that the sensitive period for effects on cocaine administration is the second week post birth [28]. After the 2 weeks treatment period, the animals are usually turned over to routine animal care. Table 1 (from Ref. [29]) describes these groups in detail. As noted above, these perinatal manipulations produce changes that are thought to endure throughout life [30,31], although some may be transient [32].

Commonly used control groups include a group reared under standard animal facility conditions (AFR) and a non-handled (NH) group, each with its own limitations [16,21]. Based on the variations in animal care across institutions, the AFR group is often criticized as a control group due to the inherent difficulties of inter-laboratory comparisons. The NH group remains untouched (with the exception of a cage change) by the animal care staff or the experimenter for the first two weeks of treatment. The NH group has been criticized by some due to the fact that the rats in this group are treated differently (during the first 2 weeks of life) from ''normal'' laboratory rats [33] although having a group that controls for both handling and separation is important. The differences in treatment during such a critical time of neurodevelopment could have serious neurochemical and behavioral effects later in life. In some studies, a group is added to control for the possible effects of handling without actually separating the litters from the dams (MS0) [29,34,35]. Brief handling of rat pups (1 min) has been demonstrated to alter such drug effects as oral morphine and cocaine consumption and preference [36,37]. Therefore, adding a group that is briefly handled in a similar manner that both the MS15 and MS180 groups experience provides a necessary control. One must be aware that variations exist in both the duration of separation and control groups used and could be a source of significant differences in findings among different laboratories. The group thought of as the control group may vary depending on the focus of the analysis. A comparison of MS0, MS15 and MS180 groups will provide ''time course'' data. Comparing NH and MS0 will show the effect of handling without separation. Finally, comparing AFR with NH and MSO will show the effects of the care given by the experimenter versus the animal care staff, without separation as a variable.

3. Effects of maternal separation and handling (MS/H) on ethanol intake

Various models of early life stress have been used to study ethanol consumption and preference (reviewed in Ref. [38]). Despite differences in methodology some overarching trends are apparent. Huot et al. [39] and Ploj et al. [40] both found that MS produced differences in ethanol intake, in male pups when they were adults. When 8% ethanol was used, MS15 and AFR groups showed similar intake, but the MS180 [39] and the MS360 [40] groups had higher ethanol intake as well as greater responses to stress. Interestingly, Huot et al. [39] showed that treatment with a selective serotonin reuptake inhibitor for 3 weeks reduced ethanol intake in the MS180s but there was no change in the MS15 or AFR rats. This has interesting implications for treatment of effects of early life stressors. Ploj et al. [40] went on to show that there were changes in several biochemical measures prior to ethanol intake that could be, at least in part, the neurochemical basis for the behavioral changes. They found greater densities of delta receptors in the pontine nuclei of MS15 and MS360 rats compared to the AFR group. Hippocampal D1 receptors were increased in the MS15 group compared to the MS360 group. There was also a noted increase in D2 receptors in the ventral tegmental area (VTA) of MS15 rats compared to MS360 and AFR rats.

A recent study on alcohol intake [29] was carried out to confirm and extend the effects of MS/H on ethanol self-administration in adulthood. Also, for mechanistic assessment, GABA-A receptors were examined in the central nucleus of the amygdala (CeA), as well as levels of alcohol metabolizing enzymes in the liver. Newborn, Long-Evans rat litters were randomly assigned to different groups and treated over PND 2–14, as described above (Table 1). Only males were studied to keep the numbers of animals to a more manageable level. In adulthood, the five groups of rats were allowed 5 days continuous access to ethanol (8%), and GABA-A receptors and liver enzymes were measured in adulthood after sacrifice. The MS15 group consumed and preferred significantly less ethanol (about one/third) than the MS180 group; in addition, neither the MS15 or MS180 groups were different from the MS0 or the AFR groups. A novel finding was that the NH group consumed and preferred significantly more ethanol than all other groups, at least twice that of the MS180s (see Fig. 1). The MS15 groups took very little ethanol, in agreement with what was found in other laboratories [39,40]. It is intriguing to see that the MS15 rats show less vulnerability to ethanol compared to other groups. Also interesting was the observation that GABA-A receptors were increased in the CeA in MS15s which could help explain the effects as these receptors have been related to alcohol intake [41–43]. Alcohol dehydrogenase (ADH) may have been altered to a small degree but only in the AFRs and is unlikely to influence the results.

Table 1 – Description of treatments of litters

	Group				
	MS15[a]	MS180[a]	NH[a]	MS0[a]	AFR[a]
Group description (from postnatal day (PND) 2–14)	Dams were separated from pups and from home cage once/day for 15 min	Dams were separated from pups and from home cage once/day for 180 min	Dams and pups untouched and left alone in home cage	Dams and pups touched to move to other side of home cage but NOT separated	Standard animal facility rearing (AFR) procedures were to transfer animals to new cages (new bedding and water) twice per week
Touch condition (from PND2–14)	YES, daily	YES, daily	Only once on PND 11, for cage change (see below)	YES, daily	YES, twice/week
Separation condition (pups from dams)	15 min/day, dams and pups to separate new cages, then returned to home cage	180 min/day, dams and pups to separate new cages, then returned to home cages	No separation	No separation	No separation but transfers to new cages as part of facility routine
Cages	AFR conditions were utilized until E21.On embryonic day 21 (E21), prior to birth, cages were changed and then left unperturbed until PND 11	AFR conditions were utilized until E21.On E21, prior to birth, cages were changed and then left unperturbed until PND 11	AFR conditions were utilized until E21.On E21, prior to birth, cages were changed and then left unperturbed until PND 11	AFR conditions were utilized until E21.On E21, prior to birth, cages were changed and then left unperturbed until PND 11	AFR conditions were utilized until E21.On E21, prior to birth, all cages were changed
	Cages, bedding and water were changed on PND 11 and some old bedding was included from dirty cage. Starting at PND 15 AFR conditions were resumed	Cages, bedding and water were changed on PND 11 and some old bedding was included from dirty cage. Starting at PND 15 AFR conditions were resumed	Cages, bedding and water were changed on PND 11 and some old bedding was included from dirty cage. Starting at PND 15 AFR conditions were resumed	Cages, bedding and water were changed on PND 11 and some old bedding was included from dirty cage. Starting at PND 15 AFR conditions were resumed	Cages, bedding and water were then completely changed on PND 5, 8 and 12. Starting at PND 15, AFR conditions were resumed
Historical notes	'Handled', in literature	'Maternally-separated', in literature	'Non-Handled', in literature	Rarely used as a control group	'Animal facility reared (AFR)', in literature

[a] Name.

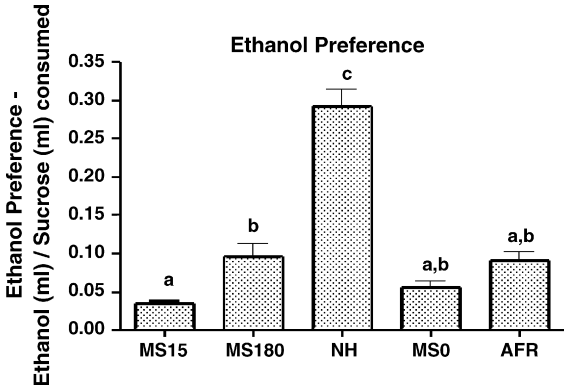

Fig. 1 – Ethanol preference among different maternally separated groups (n = 8–9 l/group). Data for each group represent mean ± S.E.M. After significant differences were found between the groups with a one-way ANOVA, individual comparisons were done using Tukey's multiple comparison test. Differences in letters on bars indicate a significant difference. a vs. b, $P < 0.05$; a vs. c, $P < 0.001$; b vs. c, $P < 0.001$; c vs. ab, $P < 0.001$; a vs. ab and b vs. ab, no significant difference. Thus MS/H treatments in the neonatal period change the propensity to SA alcohol when they are adults. This figure is from Ref. [22].

In contrast to what is seen with male rats, MS does not appear to affect ethanol consumption or preference in females [44,45]. Gustafsson et al. [44] found alterations in brain opioid and nociceptin/orphanin FQ peptides in MS animals following ethanol exposure in the nucleus accumbens and the medial prefrontal cortex, areas associated with drug reward [46–48]. Future studies are needed to understand the basis of the sex-based differences observed in ethanol consumption in animals.

Brain serotonin systems have been linked to alcohol intake [49,50]. Another recent study [35] examined serotonin transporter (SERT) levels and 5HT 1A receptor levels and function in the various MS/H groups. SERT levels were found to be changed consistently in the NH groups in several regions of brain (decreased compared to AFRs), and MS15s showed increased SERT in the amygdala. Relative changes in 5HT1A receptors were also seen as well alterations in the functional activity of the 5HT1A receptors. Thus, these perinatal treatments affect 5HT parameters [35], which may be part of the underlying mechanisms of the change in ethanol self-administration.

It is concluded that various MS/H treatments in neonates affect ethanol intake in adult male rats. The treatments also can affect opiate, serotonergic, dopamine and GABA-A receptors which are related to ethanol intake, and the treatments do not affect enzymes that metabolize ethanol to a significant extent. These changes were not simply and linearly related to time of separation, but were also due to the degree of handling.

4. Psychostimulant self-administration and MS/H

Models of early life stress have been shown to influence behaviors associated with psychostimulant drugs. Studies have shown that maternal separation alters cocaine-induced locomotor activity in rats and mice [51,52] and behavioral sensitization to cocaine [53]. Another model of early life stress, neonatal isolation, has also been shown to affect behaviors associated with psychostimulants. In neonatal isolation, the pups are separated daily from the dams similar to MS; however, unlike MS the pups are separated not only from the dam but also the littermates. Campbell et al. [54] found that in rats exposed to daily 15-min isolation periods as pups showed an attenuated conditioned place preference for amphetamine compared to non-handled controls [54]. Cocaine self-administration was also found to be altered by neonatal isolation; a daily isolation of 1 h from PND 2–9 resulted in enhanced acquisition and maintenance of cocaine self-administration [55–58].

A recent study has also examined the effects of maternal separation on the acquisition of cocaine self-administration in four separation conditions: NH, MS0, MS15 and MS180 [34]. This study did not include an AFR group due to the criticisms mentioned above. Instead, a MS0 group was included to control for the possible effects of handling in addition to a NH group. The inclusion of the aforementioned four groups allowed the experimenters to control for both the effects of handling and separation.

The acquisition of cocaine self-administration was tested after two weeks of food training using ascending concentrations of cocaine (0.0675–1.0 mg/kg/infusion). Only the MS180s acquired cocaine self-administration at the lowest dose tested. Interestingly, the MS15s did not respond for cocaine at any dose with rates greater than response rates seen for saline. At the highest dose tested (1 mg/kg/infusion) the differences between groups were similar to what was seen with MS/H studies of alcohol preference (Fig. 2). Once again the MS15s took very little drug while the NH group took the most. The decreased propensity to self-administration cocaine and alcohol observed in the MS15s is a fascinating finding and warrants further study. It is important to note that the changes in cocaine self-administration were NOT accompanied by changes in the levels of liver carboxylesterases which metabolize cocaine (not shown); thus drug metabolism does not appear to be a factor in these results. Further, rates of food-reinforced responding

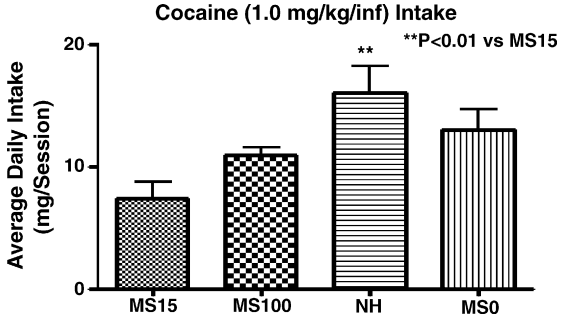

Fig. 2 – The effects of experimental treatments (Table 1) on the average cocaine intake (mg) per session of the maternally separated and non-handled adults. The data points represent the group means ± S.E.M. $^{*}P < 0.05$ NH vs. MS15 at the same dose. $^{**}P < 0.01$ NH vs. MS15 at the same dose. Significant differences were found at other doses as well. Thus, MS/H treatments alter the propensity of adult rats to SA cocaine. Data from Ref. [46].

did not differ between groups measured before and after self-administration training. Thus the MS/H treatments appear to alter the CNS drive to self-administer cocaine [34]. In summary, the MS/H model is quite interesting, robustly alters drug self-administration, produces biochemical changes and is stable and repeatable.

Because there were three different durations of separation (0, 15, and 180 min), it was shown that there was no simple, linear relationship between time of separation and cocaine intake, suggesting there are additional factors at work (related to stress perhaps). Also comparing the NH results to MS0 and other MS groups, show that handling alone has an impact and lowers cocaine intake to varying degrees. So both handling and separation in the neonatal period have impact on cocaine self-administration in adulthood.

It is notable that there were parallels between results in the alcohol SA study (Fig. 1) and the cocaine self-administration study (Fig. 2). In both, the MS15 groups took the least drug, indeed very little, while the NH groups took the most. It was not implied that cocaine and alcohol have the same exact mechanisms, but getting the same qualitative results with two different drugs of abuse, namely alcohol and cocaine, strongly supports the validity of the model for study of the general vulnerability to drugs of abuse. A goal of the field is to identify the molecular mechanisms underlying these changes, to reveal mechanisms of vulnerability to drug intake and to suggest new treatment strategies in humans.

5. Dopaminergic proteins in the mesolimbic system are changed in the MS/H animals

The dopaminergic mesolimbic system, while not the only important system for drug abuse (see for example [59]), is a focus for considering mechanisms of drug abuse. The overall evidence for the involvement of dopamine (DA) in self-administration is great and a foundation of the field [60–67]. This is particularly true for psychostimulants whose initial site of action is believed to be the dopamine transporter (DAT) [68]. Molecular changes in the DA system are thought to underlie changes in drug taking. For example, increases in DA have been associated with the rewarding effects of drugs in humans and animals, and D2 DA receptors are reduced in drug users (for example [48,69]).

Accordingly, in clarifying underlying mechanisms in MS/H, several laboratories have examined levels of various dopaminergic parameters. Brake et al. [51] found decreases in DAT levels and D3 DA receptor mRNA in the nucleus accumbens of MS180s and MS15s compared to those in the NH group. Similarly, Meaney et al. [70] also found a decrease in DAT in the nucleus accumbens of MS180 versus MS15 and NH rats. Consistent with the decrease in DAT in both of these reports, Hall et al. [71] found an increase in DA efflux by in vivo microdialysis, although their animals underwent a 6-h separation. Also Ploj and co-workers [40] found changes in opioid receptors as well as changes in DA receptors. Taken together it is clear that biochemical changes occur after MS/H and underlie the behavioral differences that are observed in adulthood.

Our studies also found changes in DA receptors, but in these preliminary studies we only examined tissues from AFRs, MS15s and MS180s, and not yet in all five groups. Ligand binding studies were carried out (Table 2), and it can be seen that the numbers of D1 receptors were significantly increased in the nucleus accumbens in both groups compared to AFRs. There was also a trend for an increase in D2 receptors in the nucleus accumbens in the MS15 group; this is compatible with the view that DA D2 receptor levels are inversely related to vulnerability to cocaine [33,48,69,72].

The observed changes in drug self-administration and the neurochemistry of the mesolimbic DA system suggest that the reward/reinforcement system in brain is altered by some conditions of MS/H. In fact, other studies support this. For example, Mathews and Robbins [25] found that maternal separation blunted a shift in the licking rate of a sucrose solution (a function of the reward system). Moreover, MS altered drug-induced changes in thresholds of intracranial self stimulation which is used a measure of central reward processes [25]. The data suggest that MS/H can cause changes in the reward/reinforcement systems in brain, although the exact mechanism is not yet understood.

6. Potential Mechanisms underlying these changes

Many groups [33,39,73–77] have proposed that the relative stress among the groups is a major factor in shaping the pups' responses as adults. In this case, stress and the neurochemical responses to glucocorticoids are proposed to somehow cause the changes in behavior by altering underlying biochemical mechanisms [16,35,40,78,79]. MS/H can change not only behavioral responses to stress but also underlying factors such as CRF, CRF receptors and glucocorticoid receptor levels [31,73,80]. MS15 rats have a lower HPA response to acute and chronic stress in adulthood compared to MS180s or NHs [70,73,76,81]. Activation of the HPA axis and subsequent

Table 2 – Data are mean ± S.E.M. percent of control (AFR value, see Table 1)

Binding site	Ligand	Region	N	MS15	MS180
D1	3H-SCH23390	Striatum	5	99.7 ± 7.69	102.19 ± 7.66
D1	3H-SCH23390	Nuc Acc	5	141.70 ± 11.11[a]	137.51 ± 10.45[a]
D2	3H-Sulpiride	Striatum	5	103.72 ± 13.22	114.05 ± 5.91
D2	3H-sulpiride	Nuc Acc	5	154.42 ± 18.16	113.20 ± 15.88

Control values (in fmol/mg tissue wet weight) were: 2.70 ± 0.14 for D1 in the striatum, 1.89 ± 0.09 for D1 in the Nuc Acc, 0.86 ± 0.14 for D2 in the striatum, 0.74 ± 0.15 for D2 in the Nuc Acc.

[a] Significant different from controls by ANOVA and post hoc tests.

release of glucocorticoids have been demonstrated to play a crucial role in the acquisition of psychostimulant self-administration [82–87]. The blunted response of the HPA axis in the MS15 group may be a factor contributing to the lower ethanol and cocaine intake in the MS15 group compared to other MS/H groups. Also, given the involvement of catecholamines in stress, it is perhaps not surprising that MS/H causes changes in the noradrenergic system (see [88] for review).

Additional evidence suggests that the reactions of the dams to MS/H and the subsequent level of care given by the dams are important and actually produce the changes in the pups [19,89–91]. Huot et al. [92], utilizing fostering of litters suggest that effects of MS may result largely from alterations in the quality of maternal care rather than from direct effects of the separation per se on the pups. Kalinichev et al. [91] reported anxiety-like behavior in dams in the MS paradigm. Also, Alberts and Gubernik [93] indicate that presence of pups to dams is necessary for normal maternal behavior. These findings are especially interesting given suggestions of changes in cocaine self-administration in dams after MS/H [34]. Moreover, it has been pointed out that the dams may not react to MS/H in the same way as the pups [51]. The hypothesis that changes in maternal care produce changes in pups is prominent in the field.

Another approach to understanding these changes could be the protein turnover approach. The level of any protein is dependent on a balance between its synthesis rate and the degradation rate. If the levels change, then one or both of those factors must change [94]. Synthesis rate, in part, is determined by rate of translation and processing of mRNAs and the resultant level of mRNAs. Degradation rate is determined by rates of internalization and proteolysis [94]. Protein levels can be routinely measured by binding techniques and autoradiography, western blotting and RIA, and mRNA levels by in situ hybridization and real time PCR. This approach could determine if the differences in receptor levels that occur after MS/H are due to changes in receptor protein synthesis or degradation or both. As mentioned above, many systems are affected by MS/H. Identifying the systems and brain regions affected contribute greatly to our understanding of drug abuse vulnerability. Studying potential alterations in receptor and transporter levels in pups exposed to MS/H at early time points may provide a timeline of neurochemical changes seen in adulthood. This would be useful for determining windows of opportunity for therapeutic intervention.

7. Epigenetic mechanisms in maternal-infant care and effects of cocaine

Cellular differentiation can be achieved through gene silencing which involves DNA methylation. This modification is very stable, maintained after cell division, and a good candidate for mediating effects of perinatal environmental stressors. For example, licking/grooming (LG) behavior in rats helps shape the stress reactivity of adult offspring [76,95]. Moreover, it's been found that different levels of LG associate with changes in the expression of glucocorticoid receptor (GR); adult offspring of low LG mothers have lower levels of GR, while higher LG mothers have higher levels of GR [75,96]. Epigenetic studies have shown that the methylation status of the GR 1(7) promoter at least partially mediates the long term effects of LG on the offspring. In low LG offspring, higher methylation of the GR promoter reduces GR expression [95,97]. This is a fascinating approach to the problem, but an obvious question is how does MS/H cause changes in methylation.

Modification of the genome in adulthood can alter behaviors. Administration of trichostatin A (TSA), a histone deacetylase inhibitor (HDAC), increases histone acetylation and remodels chromatin which leads to DNA demethylation. After a week of TSA administration, adult offspring of low LG mothers become indistinguishable from offspring of high LG mothers in their response to stress. Correspondingly, GR expression was increased and GR 1(7) promoter methylation was reduced in these HDAC treated animals [97]. Acetylation (and other modifications) of histones in the nucleosome alter the structure of the nucleosome and the ability of DNA promoters, for example, to interact with transcription factors [98]. Histone acetyltransferases (HATs) and deacetylases (HDACs) alter histones at promoters and alter gene activity or expression [99,100]. While this has been studied most in the cancer field, such changes occur in animal models, neuropsychiatric phenomena, memory and seizures [101–110].

Cocaine administration can alter acetylation specifically at H3 and H4 histones and phosphoacetylation at H3 histones [111]. Also, treatment of rats with HDACs to increase histone acetylation almost doubles the locomotor response to repeated cocaine [111]. Also interesting is that HDAC administration increased the rewarding effects of cocaine measured in the conditioned place preference paradigm, and conversely, over expression of HDAC4 in the striatum reduced the rewarding effects of cocaine [111]. This opens the possibility that MS/H treatments induce epigenetic changes which underlie at least some of the behavioral effects and may help explain the long lasting nature of these effects.

8. Prospects for development of medications and treatments

Several interventions have been shown to affect various sequelae of variations in MS and handling. Francis et al. [112] found that environmental enrichment during the peripubertal period completely reversed the effects of MS on both HPA and behavioral responses to stress, but with no effect on CRF mRNA expression. It was therefore concluded that environmental enrichment leads to a functional reversal of the effects of MS through a compensation for, rather than through a total reversal of all neural effects. Studies have shown that treatments with antidepressant drugs can reverse some effects of MS and variations in handling in the perinatal period. For example, MacQueen et al. [113] showed that chronic treatment of MS mice with desipramine prevented changes in swim times and BDNF levels, and Huot et al. [39] reported that treatment with paroxetine for 21 days eliminated differences in responsiveness of the HPA axis and reduced the amount of ethanol intake in an MS group. Overall, these findings suggest that this MS/H model may be useful for identifying treatments that may be worthwhile testing in human populations.

9. Validity of the MS/H model

When using animals to model a human condition it is important to consider the model's validity. Animal models are often evaluated on three criteria: (1) face validity: does the animal model display similar symptomatology as the human condition the model is based on? (2) predictive validity: does the model predict what it is theoretically supposed to predict? (3) construct validity: is the model theoretically sound, are the variables measured associated with the trait being modeled? [114,115]. This review is concerned primarily with the ability of the MS/H model of early life stress to provide information on possible neurochemical factors that contribute to an increased vulnerability to drug abuse. The increased vulnerability to drug abuse is, in this case, measured by drug self-administration, which is considered a valid predictor of human drug use [1–3]. Evaluating the face validity of the MS/H model in the context of drug abuse in that the symptomatology of individuals susceptible to drug abuse is not always clear. MS/H has good predictive validity in that it predicts that early life stress affects vulnerability to drug abuse. Clinical studies have shown a strong relationship between adverse early life experiences (i.e. household dysfunction, physical and/or sexual abuse) and drug abuse [116–118]. Finally, the MS/H model has suitable construct validity in that the procedures of MS/H are theoretically sound and reasonable. Exposing rat pups to early life stress or adverse early life experience causes profound neurochemical and behavioral changes that last into adulthood.

10. Summary

Taken together, data from many labs clearly show that variations in MS/H treatment create differences in drug self-administration in offspring when they are adults. While the focus here is on drug abuse as an example, other reviews and papers cover various other aspects of the effects of MS/H [11,27,30,38,70,76,89,119–122]. Further, neurochemical changes in neurotransmitters, particularly dopamine and serotonin, have been found that may underlie the changes in drug self-administration behavior. Thus, biochemical pharmacologists must consider perinatal conditions as a potential source of changes in various biochemical parameters. Moreover, these neurochemical changes, like the behavioral changes, endure presumably throughout the lifetime of the animal. Understanding the mechanisms of these changes may lead to new treatment strategies for humans.

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