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Similitude in Methamphetamine-Induced Neuroadaptations Across Susceptibility and Chronic Drug Exposure Paradigms

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The study by *Szumliniski et al.* (1) in this issue of *Biological Psychiatry* investigates molecular correlates of methamphetamine addiction, with a focus on the glutamatergic system in the nucleus accumbens. This article, whose title echoes that of the classic spaghetti western film, is unique in that it finds commonality in the altered states of the accumbens glutamate system of populations susceptible to methamphetamine addiction as well as in populations chronically exposed to the drug.

In the first part of the study, Szumliniski *et al.* (1) employ a methamphetamine-infused drinking water paradigm whereby mice orally self-administer the drug. Through selective mouse breeding, two subsets of animals emerge, those that drink more of the solution (methamphetamine high drinking [MAHDR]) and those that drink less (methamphetamine low drinking [MALDR]). This split establishes a platform to investigate alterations in glutamate signaling that may underlie methamphetamine addiction or vulnerability to addiction, a strategy used throughout the study in several different permutations. The investigators find that compared with MALDR animals, the MAHDR animals display a higher level of basal extracellular glutamate and increased expression of metabotropic glutamate receptor 5 (mGluR5) and Homer2a/b in the nucleus accumbens. This result resonates well with the Gass *et al.* (2) study that demonstrated that antagonism of mGluR5 inhibits reinstated methamphetamine seeking. Furthermore, the data presented in the current article fit well with previous studies from the same group demonstrating the involvement of Homer2a/b in drug-related behaviors (3,4). Finally, knockout animals for Homer2 and mGluR5 further support a role for these proteins in addiction (5,6). As Szumliniski *et al.* (1) elucidate differences in the accumbens glutamate systems of these two populations of animals, their study brings to mind an intriguing set of questions regarding how these changes in protein expression are enacted. It is immediately apparent that it must be due, at least in part, to the higher levels of drug exposure in MAHDR animals. It follows then that drug-induced alterations in protein expression start to take place in subjects exposed to higher levels of methamphetamine and are then likely passed onto progeny via some form of epigenetic imprinting (7). This raises the possibility for future studies aimed at investigating possible differences in histone protein modifications at the mGluR5 and Homer2a/b loci in the nucleus accumbens of MAHDR versus MALDR animals. If differences in histone modifications at these genes were found, could reversing them turn an MAHDR subject into an MALDR subject? Would these differences be specific to male or female subjects?

However, it is important to note that it is also entirely possible that the changes to Homer and mGluR5 expression are occurring as a result of alterations to factors that regulate the transcription, translation, or trafficking of these proteins as opposed to the chromatin state of the genes themselves.

In a second arm of their study, Szumlinski *et al.* (1) investigate methamphetamine conditioned place preference (CPP) or conditioned place aversion (CPA). In short, the majority of animals show a preference for the drug-paired environment, whereas a smaller portion show aversion, and finally a set of animals are neutral. This paradigm, like the selective breeding paradigm discussed above, is utilized as a platform to investigate altered aspects of the accumbens glutamate system linked to methamphetamine-related behaviors. Akin to what was observed in MAHDR versus MALDR animals, mice that show methamphetamine CPP selfadminister more methamphetamine, take longer to extinguish this behavior, and display higher levels of reinstated methamphetamine seeking. With regard to the accumbens glutamate system, methamphetamine CPP animals, like MAHDR animals, display elevated levels of mGluR5 and Homer2a/b in the nucleus accumbens, yet unlike the MAHDR animals also show elevated levels of mGluR1. In further investigation of the CPP, CPA, and neutral animals, Szumlinski *et al.* (1) report that levels of Homer2a/b, mGluR1, and mGluR5 correlate with CPP score, being higher in CPP animals and lower in CPA animals with neutral animals in the middle, suggesting a causative role for these biological changes in the CPP-CPA continuum. Again, these results are highly consistent with others from the same group, demonstrating elevated Homer2a/b levels in animals that binge drink alcohol (8), and fit nicely with the emerging theme that Homer proteins are involved in addiction not only of methamphetamines but also of other classes of addictive substances.

In keeping with the MALDR/MAHDR and CPP/CPA dichotomy and the similarity of the biological differences between the groups, it would be interesting to determine whether selective breeding causes alterations in the number of animals that display CPP versus CPA. For example, one would expect to have higher levels of CPP animals in an MAHDR cohort when compared with an equal number of MALDR animals. This would be a highly interesting variable to track as the MAHDR population developed through successive generations. Moreover, this brings to mind the following question: Does the selective breeding intensify the higher drug-intake phenotype along a continuum or is it a binary change? Given the correlation data shown in the CPP versus CPA animals for mGluR1, mGluR5, and Homer2a/b, one would expect it to be the former. Moreover, would the split of CPP versus CPA animals also drift toward CPP as successive generations of MAHDR animals are generated? Are there any sex differences in this phenomenon?

As described above for MAHDR versus MALDR and CPP versus CPA, a methamphetamine versus saline injection protocol (10×2 mg/kg intraperitoneally, once daily) combined with 21 days of forced abstinence (withdrawal) is used as a third and final set point for investigating biological differences in the expression of proteins of interest in the nucleus accumbens. Szumlinski *et al.* (1) demonstrate that animals that received repeated drug injections have higher baseline extracellular glutamate following 21 days of withdrawal, similar to what was reported for MAHDR animals. The investigators determine that this effect is not occurring due to alterations in either sodium-dependent or -independent

accumbens glutamate clearance, which is a particularly interesting given that glutamate uptake is negatively impacted by other drugs of abuse in this brain region (9). When given a methamphetamine challenge (1 mg/kg), animals that had undergone methamphetamine treatment and withdrawal showed enhanced glutamate levels in the accumbens, which is again strikingly consistent with what was observed with the MAHDR animals. In the context of the extant literature, this finding also fits nicely with others reporting enhanced extracellular levels of accumbens glutamate during methamphetamine primed reinstatement following extinction training (10).

Taken together, there is a remarkable amount of overlap with the MAHDR, CPP, and methamphetamine-injection and -withdrawal animals with regard to the biological endpoints presented in the study, underscoring the relevance of these adaptations in methamphetamine-related behaviors. Toward this end, one commonality among all three groups is enhanced expression of Homer2 in the shell subcompartment of the nucleus accumbens. In the final series of experiments, Szumlinski *et al.* (1) demonstrate that this elevated level of Homer2 is responsible for elevated methamphetamine intake in animals with a history of drug exposure. This was performed after the daily treatment and withdrawal, whereupon animals received intra-accumbens shell infusions of an adeno-associated virus-Homer2–short hairpin RNA or control vector. Szumlinski *et al.* (1) report that short hairpin RNA–infused animals show decreased CPP for methamphetamine as well as reduced effort expenditure (in this case, nose poking as an operant response) for methamphetamine on an FR5 schedule of reinforcement, which also translated into lower methamphetamine intake on this schedule. A dose-response analysis revealed that the Homer2–short hairpin RNA group also displayed lower drug intake at lowest doses of methamphetamine tested (5 and 10 mg/L).

In summary, methamphetamine-experienced animals and animals susceptible to methamphetamine addiction show similar adaptations in several proteins in the nucleus accumbens linked to drug addiction. The report by Szumlinski *et al.* (1) in this issue of *Biological Psychiatry* finds commonality across a diverse set of treatment paradigms, culminating in an elegant demonstration of the importance of Homer2 expression in a specific subregion of the nucleus accumbens that may represent a mechanism underlying methamphetamine intake and use vulnerability. In addition to the central finding of the study, these experiments also open doors to exciting future experiments aimed at understanding precisely how drug exposure and the genetic background for methamphetamine susceptibility are linked at the molecular level.

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