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Reviewing Self-Injuries Behavior in Macaques: The Role of Early Experience and Genetics in an Integrated Non-Human Model

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ABSTRACT

Genetic differences in non-human primates and the context where they were reared are important in the determination of their behaviors. Some studies suggest that Self-Injurious Behavior results from stress or anxiety, but some macaques appear to be more vulnerable to acquiring Self-Injurious Behavior. Vulnerability and risk for socially reared macaques of developing Self-Injurious Behavior increased when they experienced early adverse events and suffered from consequent stress. Stressful events can cause alterations in the neuroendocrine and neuropeptide systems associated with the regulation of stress and anxiety. Dysregulation in these systems contributes to the occurrence of anxious episodes that lead to self-harm. This could be used by those animals to counteract the effects of anxiety, causing euphoria by releasing endogenous opioids. In developing an integrative approach of Self-Injurious Behavior, we propose the diathesis-stress model to illustrate how the environment and genetics are influenced as well, taking rhesus monkeys as an example. Rhesus macaques and humans have essentially the same gene 5-HTT as well as functional polymorphism. The allelic variation in the region promoting the serotonin transporter gene (5-HTT) was associated with significant differences in the number of depressive symptoms and contributions to social reward and punishment. Growing up without the mother and the rearing environment are important risk factors for developing abnormal behaviors. The main idea is that monkeys who carry short 5-HTT allele and are reared with their peers (without their mother) suffer from neurobiological developmental delay, deteriorated serotonergic functioning and act more aggressively. Monkeys who carry short 5-HIAA allele and are reared with their mothers, though, show normal behavioral patterns. We could conclude that carrying the short allele of gene 5-HTT leads to a psychopathological tendency in macaques with a poor parenting history, but it may be adaptive for those who establish an attached relationship with their mothers. Stressful early experiences result in impaired 5-HTT expression as well. There are both specific genetic and environmental factors which pose a risk in the development of adverse responses to stress and environment. Rhesus macaques, as well as humans, show big individual differences in their responses to environmental stress. Some are very fearful and anxious, others are aggressive and impulsive. It is possible to identify genetic and environmental patterns that contribute to these differences, but recent evidence suggests that the interaction between genes and environment is of equal importance.

KEYWORDS

5-HTT; Primates; Allelic Variation; Diathesis-Stress Model; Self-Injurious Behavior; SIB

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1. Introduction

"Self-injurious behavior" (SIB) is understood as any self-inflicted act causing tissue damages [1]. They can occur as cuts, burns, bites, etc. [2], although it doesn't require an injury to categorize an action as self-injurious when there is a potential danger [3].

SIB is often used to reduce stress or anxiety [4-9], whereas stress management was identified as one of the reasons for the appearance of this behavior in 77% of a clinical sample that had suffered a previous trauma [10]. Furthermore, Symons *et al*. [11] found a significant positive correlation between salivary cortisol levels and the severity of SIB in adults with developmental disabilities, supporting the possible relationship between stress and self-harm.

This behavior is not exclusive to humans. A small percentage of monkeys in captivity also showed them in a study [12,13]. In fact, an animal model that has been studied extensively is the rhesus macaques as it is not based on any principle of social isolation or biological or chemical manipulation. Thus it is more likely that they share with humans some of the etiological and physiopathological factors that contribute to the development of self-harm [14]. In addition, macaques and humans share between 90 and 94 percent of their genetics [15] and have a similar endocrine and neurophysiological system as well as social complexes, hierarchies and environmental experiences [16,17]. Another reason why the animal model is useful when considering SIB is that their environment can be controlled; thus the non-human primates provide a valid model of understanding the origins of the interaction between early adverse experiences and functional genetic variants in the development of stress-related disorders [18,19].

To understand the singularity of the example of rhesus macaques, it is noteworthy that studies with other family members of macaques show no functional polymorphism of the 5-HTT gene [20] or MAO-A [21]. Furthermore, another characteristic shared only by humans and rhesus macaques is that they can live in a wide range of habitats and social environments, presenting great adaptabilities [22].

2. Biological Correlates

It is important to understand what biological correlations there are behind SIB and its utility to the subject. Thus, on a physiological and neurochemical level, some studies indicate that macaques exhibiting SIB have long-term alterations in the central and peripheral opiods and in their stress-response-systems, which causes higher levels of anxiety [14]. It seems that there are various biological systems implicated in the expression and upholding of this kind of behavior in humans, including the endocrine and the central monoamine systems [23,24]. Specifically identified to play an important role in the expression of self-harm have been dysregulations in central serotonergic neurotransmission (5-HT) [25,26] and/or dopaminergic [27-30], and also central opioid and peripheric systems [26,31,32].

Some studies suggest that SIB in socially reared macaques is associated with complex changes in the function of the Hypothalamic-Pituitary-Adrenal (HPA). It is also noteworthy that plasma cortisol levels correlated negatively with the frequency of self-biting, which is suggesting a connection between the main expression of the disorder (self-biting) and observed HPA dysregulation [33].

There are two main hypotheses about central and peripheral opioids [23,24,26,34,35]. The hypothesis of self-administration of opiates—or hypothesis of addiction—indicates that individuals with SIB believe that they are addicted to the release of endogenous opioids and for that reason they harm themselves [34,36]. The second hypothises—called the pain hypothesis—argues that a high endogenous opioid activity increases the pain threshold (hypoalgesia) [37]. Thus they feel no pain during SIB and possibly do it as a form of self-stimulation [34]. It has been shown that rhesus macaques, which exhibit self-harm, direct their biting to body parts related to analgesia, produced by acupuncture or acupressure [38].

Furthermore, most of the related studies with animals and humans suggest that an increased activity of the noradrenergic system gives occasion to aggressive behavior. Additionally, a downregulation of the density of postsynaptic noradrenergic receptors in the prefrontal cortex has been demonstrated in postmortem tissue of suicides, possibly happening after an increased release of this neurotransmitter [39].

Gene-Environement Interaction

Researchers such as Caspi, Moffit and colleagues demonstrated that the allelic variation in the region promoting the serotonin transporter gene (5-HTT) was associated with significant differences in the number of depressive symptoms, but only if there was neglect or abuse during childhood or if the subject was experiencing high levels of current stress [40]. Another survey shows that genetic variation in serotonin function contributes to social reward and punishment in rhesus macaques, and thus shapes social behavior [41]. Rhesus macaques and humans have essentially the same gene 5-HTT as well as functional polymorphism [42].

Several studies have shown that individual differences in concentrations of 5-HIAA are highly hereditary between macaques of similar age and upbringing [43]. Moreover, both types of 5-HIAA concentrations in the

cerebrospinal fluid and its corresponding behavioral correlation are due to significant modifications through early social experiences, particularly those related to attachment [44].

Recent researches have demonstrated significant interactions between specific genetic factors and life experience in rhesus macaques. For example the serotonin transporter gene (5-HTT) has a length variation resulting in an allelic variation in hisexpression. A heterozygous short allele (long-short) provides a low efficiency of the transcription to the 5-HTT promoter compared to the homozygous long allele (long-long) being more likely that a low expression of the gene can result in a decrease in the serotonergic function [45]. Also there are researches which suggest that polymorphisms in the gene encoding the 5-HT transporter modulate the adverse consequences of social subordination on the timing of puberty in female rhesus monkeys [46]. Polymorphisms in this gene may even contribute to differences in reproductive compromise in response to chronic stress [47].

Early environments involving factors such as childhood physical/sexual abuse may prove useful for explanation of the personality disorders concept based on gene-environment interaction [48]. Many studies argue that the expression of 5-HTT is relevant to the relationship between early life stress and impulsive behavior, holding even this relationship is observable at an early stage in the development of rhesus macaques [49]. A body of literature suggests that stressful early experiences result in impaired 5-HTT expression [50-54].

Macaques being carriers of the short allele of the 5-HTT gene show an early retardation in their neurobiological development, deteriorated serotonin function and excessive aggressiveness, but only if they were bred with their peers without their biological mother. Those who are raised with their biological mother and carry this allele show normal development patterns [55-58]. In addition, the monkeys reared by their mothers who carry the short allele consume less alcohol than those reared by their mothers but carrying the long allele, which tells us that carrying the less efficient allele can be a risk factor for monkeys raised without their mothers, but a protective factor for monkeys raised by their biological mothers [59].

A similar pattern occurs in relation to aggressiveness: macaques reared with their peers with long-short allele showed high levels of aggression while those reared by their mothers carrying the same allele were compared with long-short allele (both those raised by their mothers and those raised by their peers) suggesting, again, a compensatory effect of maternal parenting [60].

Champoux *et al.* [61] found out that infant macaques that carried the long-short allele and were reared in laboratories without their mothers showed significant deficits in attention, activity and motor maturity in relation to those raised as well without their mother but carrying the long-long allele. On the other hand, infant monkeys with long-short allele and long-long being reared by their biological mother showed normal values [61].

We could conclude that carrying the short allele of gene 5-HTT leads to a psychopathology in macaques with a poor parenting history, but it may be adaptive for those who establish an attached relationship with their mothers [44].

Another gene whose allelic variation has been studied in relation to the interaction between genes and the environment and the presence or absence of a history of rejection and/or abuse in childhood is the MAO-A. An interpretation of Caspi and colleagues about the polymorphism of the MAO-A is that the most efficient allele protects individuals, who carry it, from possible effects of aggressive behavior resulting from early adverse experiences like rejection or abuse in childhood [40]. In other words: a “good” gene offers protection against a “bad” environment [20].

Gathering all the data from these studies, it seems clear that there are specific genetic and environmental factors which pose a risk in the development of adverse responses to stress and environment [44]. Some authors suggest that genetic or environmental factors may mitigate the risk for behavioral dysregulation illustrated in the patterns of behavioral activity and emotional reactivity displayed by infants [62].

3. Diathesis-Stress Model

In developing an integrative approach of SIB we propose the diathesis-stress model as a psychological theory that can explain this behavior as a result of genetic vulnerability together with stress from life experiences from an evolutionary point of view.

3.1. Vulnerability: The Role of Early Experiences in the Diathesis-Stress Model

Some macaques appear to be more vulnerable to acquiring SIB. Data obtained through the records of a rhesus macaque colony suggests that this higher vulnerability and risk for socially reared macaques of developing SIB increases when they experienced early adverse events and suffered from consequent stress [14]. Monkeys with SIB also have a dysregulation of the HPA axis, indicated by a blunted cortisol response to mild stressors [63].

Likewise, Tiefenbacher *et al.* [33] consider that some animals could be predetermined for the development of SIB and, at the same time, exhibit alterations in the function of the HPA system. On the other hand,

it seems that stressful life experiences such as early separation from the parents or numerous veterinary consultations are risk factors for the development of this behavior [63-65].

Several factors influence the development of abnormal behavior in animals in captivity, but an interruption in their early upbringing seems to be the most important contribution to the development of behavioral problems [3,63,66-69]. Individuals raised by a nanny seem more prone to develop abnormal behavior than those reared by their mothers [3,63].

Growing up without the mother and the rearing environment are important risk factors for developing abnormal behaviors [3,70,71]. Some studies suggest that some of these behaviors may be established before the socialization begins. Thus, the lack of early tactile stimulation and responses to distress in childhood may be factors in the development of abnormal behaviors [71].

Other studies indicate that there are further risk factors for the development of self-harm [3,63,66,72]. In the case of self-inflicted wounds, several of these factors are related to individual cages, the age at which they have been caged for the first time [3,63,72]and the total caging duration [3,72].

Lutz *et al*. [3], following researches conducted decades ago by Harlow and Harlow [73], argue that the best predictor of SIB is a poor early rearing experience. Monkeys brought up without the company of members of their species during the first six months of their life developed generalized patterns of anomalies known as "isolation syndrome", which comprise a more emotional, inappropriate social behavior, inadaptability to new situations and an extensive repertoire of behavior disorders [74].

Another factor to consider in the expression of self-harm is the exposure to stressful events, which can oscillate from an increase of the sound level, altering the sense of balance in chimpanzees [75], up to changes in breeding schemes, which can cause an increase in stereotyped movements in macaques and squirrel monkeys [76,77].

3.2. Stress and/or Anxiety

As in humans [78-80], anxiety is an important factor in the expression of SIB in monkeys reared in society according to results of studies in colonies. Treatment with Diazepam produced a significant decrease in self-inflicted bites and the occurrence of injuries in half of the monkeys. However, this treatment increased the occurrence of injuries in the remaining animals from New England Primate Research Center (NEPRC) colonies that were also treated with Diazepam [81]. The evaluation of the records of the colony indicated that animals with a positive response to the treatment had spent more time individually housed and had experienced a greater number of minor veterinary interventions than those who had a negative response. These results imply the existence of two types of monkey populations with SIB: those whose behavior arises from life experiences and who are sensitive to treatment with anxiolytic drugs, and those whose behavior is related to other factors (*i.e.* genetic) and who do not respond to anxiolytic treatment [14].

A probable stressor for these animals, in addition to captivity, is the relocation of their homes, as several studies have shown that this causes a cortisol response [82]. A study by Davenport *et al.* [2] with rhesus macaques shows *that there are behavioral and physiological changes in male monkeys who suffered from stress when relocated. In fact, the stressor caused a pathological response in ani*mals with particularly strong SIB, significantly increasing the frequency of disruptive self-bites and sleep disorders. The results show that this behavior may be exacerbated by stress in this animal model and those stressful events lead to the development and maintenance of this pathological behavior [12,14,83].

3.3. Individual Differences

Not everybody responds the same way to similar stimuli. It has been found about 20% of the monkeys react to not very stressful social situations with an unusual pattern of fear and anxiety, accompanied by a prolonged activation of the HPA axis. In turn, about 10% of the population shows impulsive and/or aggressive behavior under similar circumstances, demonstrating a dysfunction in serotonergic activity [20].

But how do these differences develop? Rhesus macaques grown in the wild spend the first month almost exclusively with their mother. In their second month, the hatchlings begin to explore their physical and social environment, using their mother as a "safety base". In the subsequent weeks and months, they are spending more time away from their mothers, beginning to build relationships with other group members (mostly of their own age). Throughout the rest of their childhood, they are spending several hours a day in this social game with peers, what is important in the development of a normal functioning adulthood. Aggressive hatchlings often show violent behavior during this social game, starting combat games that end in physical violence against their fellow players. Both the anxious and the aggressive rhesus macaques tend to show significant deviations from this pattern of social development starting at a very early point in their lives. Anxious hatchlings begin to separate from their mothers much later and show a lower ratio of exploratory behavior than the rest of their peers. They spend less time playing with other macaques of the same

age, and when they are physically separated from their mother, they demonstrate a high degree of anxiety, accompanied by high and prolonged levels of cortisol [20,84]. Several studies show a significant genetic component to that [85,86].

Parenting Schemes

Macaques reared without their mother developed a strong attachment among them in only a few days. This attachment is not functional because a peer is not able to fulfill maternal functions (protection, calm, etc.) [87]. Additionally, those reared without their biological mother showed less significantly concentration of 5-HIAA in the cerebrospinal fluid from childhood to early adulthood [88,89].

We can conclude that macaques reared without their biological mother show the same behavior and biological patterns as a response to the environmental and social stress as anxious and aggressive monkeys. Early social experiences have consequences for the rhesus macaques both in their biological development and behavior, far beyond genetics [20].

4. Conclusions

Because a brain in development shows more plasticity and responses to environmental changes than an adult brain [90], early detection may be the best strategy as a remedy. In any case, a combination of social enrichment, use of positive reinforcement, increasing control of an animal's environment and improving parenting techniques for the ones without their biological mother may be the best solutions for these anomalous behaviors [71].

Since there is no hypothesis that can fully explain SIB, Tiefenbacher *et al*. [14] propose an integrated hypothesis of the origin and maintenance. It suggests that early adverse experiences, followed by stressful events, can cause alterations in the neuroendocrine and neuropeptide systems associated with the regulation of stress and anxiety. Dysregulation in these systems contributes to the occurrence of anxious episodes that leads to self-harm. This could be used by those animals to counteract the effects of anxiety, causing euphoria by releasing endogenous opioids.

We would like to add that rhesus macaques, as well as humans, show big individual differences in their responses to environmental stress. Some are very fearful and anxious in response to changes in their environment, others are aggressive and impulsive. One can identify genetic and environmental patterns that contribute to these differences, but recent evidence suggests that the interaction between genes and environment is of equal importance, possibly through mechanisms by which specific aspects of the environment influence the expression of certain genes at specific times of development [20].

The association between behavioral trait measures collected early in life and later social adaptation and personality in adult non-human primates is only beginning to be understood [20,91-94]. In humans, behavioral disinhibition measured early in life is a known predictor of impulsivity and aggression in adolescence and adulthood [95,96]. If this is also true for non-human primates, 5-HTT plays a role in the "cycle of violence" phenomenon observed in humans and rhesus macaques [49,97-99].

In this context, the animal model that helps us to understand self-harm is the Diathesis-Stress Model. We take rhesus macaques, who share 95% of their genes with humans and who possess a similar adaptive capacity, as an example. Other species like chimpanzees that share more than 98% of their genes with humans have the monozygotic gene. So why did we choose rhesus macaques as our integrated model? Rhesus macaques have short and long alleles of the serotonin transporter gene like humans; they share with humans the same biodiversity. In both of them, the childhood environment plus the individual genetic determinates the level of violence in later life coping with stress. In this sense, although humans and chimpanzees share more genes, rhesus monkeys and humans possess a bigger similarity: the biodiversity in the individual behavior regarding impulsivity and aggression. This peculiarity is what makes them more versatile in their adaptation capacity.

Having a negative emotional experience with caregivers during childhood precipitates the development of an abnormal mental model about relations, which continues manifesting during adulthood. Relationship with early caregivers decisively influences the way adults maintain relations afterwards. If these first contacts are insufficient or anomalous in some way, there will be repercussions in later social life [48].

Furthermore, early environments may play an important role through their influence on psychobiological functions in adulthood [100,101]. Contributing to the information about the kinds of environment, the organism will have to be dealt with in the future. In addition, there are several studies that highlight the correlation between the serotonin transporter gene and stress [104-109]. Again, recent work has succeeded in delineating some of the specific psychobiological factors that underlie such programming, including both genetic and epigenetic mechanisms [102,103].

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