Evidence for a link between early life stress and adult aggression – The role of the hypothalamus-pituitary-adrenal axis

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Early-life stress (ELS) is told to participate in the emergence of many psychopathologies during adulthood such as PTSD or depression. In order to understand better the consequences of an ELS in the adulthood, many models have been established. One of the main models used in different species is the separation of the child from his mother during childhood. The hypothalamo-pituitary-adrenal (HPA) axis is the main axis regulating the stress response in Mammals. All studies agree in underlying that the components of this axis are altered after an ELS. Furthermore, different studies in rodents as in primates have shown that the different components of the HPA axis, such as the vasopressin, may play an important role in the emergency of aggression in a sex-specific manner. Thus, it is essential to understand how the alterations of the HPA axis induced by an ELS, such as repeated maternal separation, may induce alterations in aggression in adulthood.

Introduction

Early life stress (ELS) corresponds to a wide range of events which can happen during early childhood: child abuse, neglect and trauma, parental loss due to a death or a divorce or also consumption of drugs during pregnancy. Because of this variety, many models have been used as well in terms of animals: rhesus macaques, common squirrels, rats, mice, guinea pigs, hamsters, as in terms of type of ELS: repeated or definitive mother-infant separation (MS) at different periods of the development, early post-weaning social isolation, post-weaning social subjugation. All kinds of ELS seem to alter the hypothalamo-pituitary-adrenal (HPA) axis and adult aggression. There are different kinds of aggression. As reported by Veenema [1], the main types of adult aggression are: *offensive aggression* when competing for or protecting resources like food, territory and mating, *defensive aggression* when the animal is attacked by a conspecific or a predator, *predatory aggression* for predators when attacking a prey and *maternal aggression* for the mother protecting her children against an intruder. Each type of aggression differently interacts with the HPA axis and is thus differentially affected by an ELS. Stress is a characteristic reaction linked to something potentially dangerous for the organism. Stress can be whether psychological (fear) or physiological (hypoglycemia, blood loss) or both (lack of mother).

Many studies report a direct link between the development of the HPA axis and ELS. Fewer focus on the link between this phenomenon and adult aggression. Firstly, we will see when ELS affects the HPA axis development. Then we will characterize the consequences of ELS on the child's and on the adult's HPA axis. Finally we will study how this alterations can affect the different kinds of adult aggression. To do so, we will focus on the main models of ELS studied which are rhesus macaques, rats and mice after a separation from the mother during early childhood. Early-life corresponds to the period going from fecundation to the end of puberty. Here, we will only consider it as the period going from birth until puberty, in the frame of this model of MS. This model mimics early parental loss or neglect of the child.

On what period of the HPA axis development does this model have an impact?

How does the HPA axis normally develops in the different animals studied?

The HPA axis consists in the paraventricular nucleus of the hypothalamus, the anterior part of the pituitary gland and the adrenal cortex (Figure 1.A). The hypothalamus and the pituitary gland mostly develop during prenatal stages of the development [2]. The adrenal gland begins its development prenatally but it still needs some time postnatally until it is fully developed. The adrenal cortex ends its maturation between 10 and 20 years in humans and at post-natal day (PND) 35 in mice [3]. Very interestingly, in rodents, the hippocampus, a major factor interacting with the HPA axis (Figure 1), develops from PND 1 to 21 [4]. In primates, it develops in the first years of life. Thus, an ELS during childhood might influence the development of the hippocampus and of the adrenal gland.

In rodents, a certain period named as the stress hyporesponsive period (SHRP) is necessary for the normal development of the brain after birth. It corresponds to a period when a stressor which would normally involve a physiological stress response (increase of glucocorticoids and adrenaline, rise of the cardiovascular tone, modifications of the immune system) has no effect. This period lasts from PND 2 to 12 in mice and from PND 4 to 14 in rats [5], PND 1

being the date of birth. It is mediated through maternal physical care. Indeed, it has been proved that depriving the pups from their mother can disrupt the SHRP [5]. Using a brush on the pups to imitate the maternal care can partly reverse this effect [6–8] while letting the pups see and smell their mother without physical contact does not. Maternal care effects in rodents come from arched-back nursing, licking and grooming [5–8]. Further studies remain to be done on primates to see whether the SHRP is a conserved process among species or if it is specific to rodents. An old study [9] suggests that there is a SHRP in humans from 12 month old and on. Nevertheless, they have not determined how long it lasts.

The normal adult HPA is regulated by the circadian rhythm (Figure 1. A,C) and by the environment (Figure 1. A,B), especially by stressful events, whether they are physiological and/or psychological (see Figure 1 to look at all the components). The end-products of the HPA axis are the glucocorticoids (GCs). In rodents, the principal GC is the corticosterone while in humans and rhesus monkeys, it is the cortisol. GCs mediate the stress response and a negative feedback (Figure 1). The negative feedback aim is to stop the stress response once the stressor is gone.

The HPA axis develops partly prenatally and partly postnatally during the first weeks/years of life. In rodents, a SHRP is necessary for the postnatal development of the axis, but it has still not been identified in primates. MS might influence the postnatal development of the hippocampus and of the adrenal cortex.

What are the different models of MS studied?

As there are so many types of ELS and as much models representing them, we chose here to focus on the main model studied: repeated MS during the SHRP in rats and mice and definitive or repeated separation just after birth in rhesus monkeys. In humans, this could correspond to maternal or parental loss due to an accident or a divorce or to a parental neglect of the child.

It is first essential to pinpoint the slight differences of the protocols between the different models so as to understand the further differences which can appear. Generally, in rodents, the MS consists in taking the dam away from her pups for 3 hours every day, generally from 9am to 12pm, during the SHRP and sometimes a little further of the SHRP. Meanwhile, the pups are handled in an other cage all together with an incubator imitating the mother's heat. This protocol is quite respected among the different studies. It partly comes from the article of Huot *et al.* [10]. Some test longer or shorter time of separation at different periods (see [5] for review). Sometimes also, pups are left in their homecage all together or handled and separated from each other. It has been reported that this slightly different protocols may affect the pups in a different manner [11]. However, the problem remains on the control used. The results might be quite different whether the control used is undisturbed pups remaining all the time with their mother (non-handled) or just a little handled to clean the cage once a week (animal facility rearing) or pups handled from their mother for only 15 minutes every day. The last one might be closer to the wilderness where the mother might have to let her pups to search for food [5]. On the other side, there might be a bias as the interaction between the

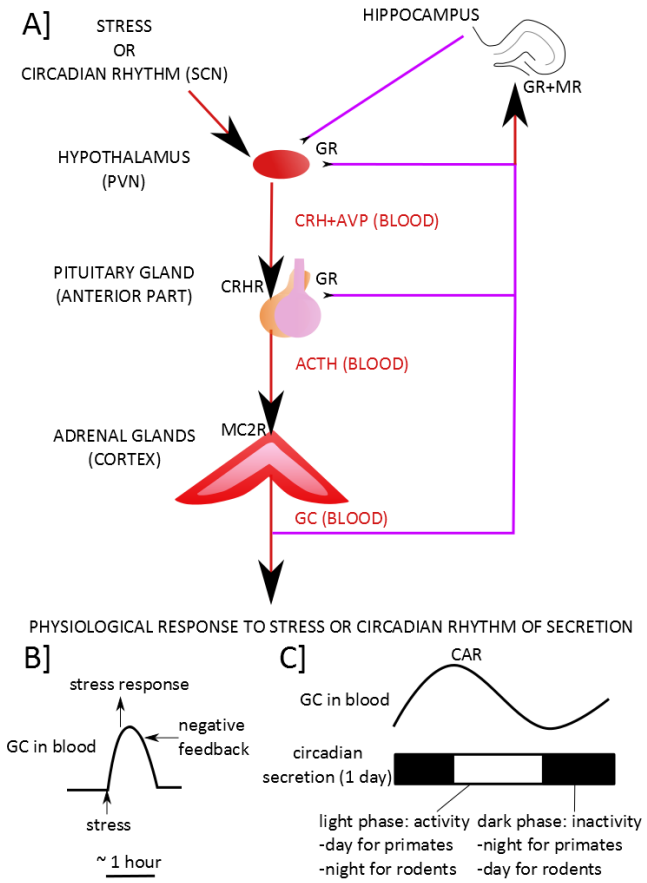

Figure 1. The normal functioning of the HPA axis. A] An external stressor or the influence of the projections coming from the suprachiasmatic nucleus (SCN) which regulates the circadian rhythm induces the expression and the release of the cortico-releasing hormone (CRH) and the vasopressin (AVP) by the paraventricular nucleus (PVN) into the portal blood supply of the anterior pituitary gland. The CRH binds to the CRH receptors (CRHR) in the anterior pituitary gland. In the anterior pituitary gland, the AVP enhances the action of CRH. The CRH, when binding to the CRHR, induces the synthesis and the release of the adrenocorticotropic hormone (ACTH) in the blood. ACTH binds to the melanocortin type II receptors (MC2R) in the cortex of the adrenal gland. This binding induces the synthesis and the release of corticoids in the blood. The corticoids induce some physiological modifications. They also activate the negative feedback of the HPA axis directly by inhibiting the secretion of the pituitary gland and the PVN and indirectly by activating some neurons of the hippocampus which will then inhibit the PVN. **B]** The corticoids induce the physiological response to the stress in response to a stressor. **C]** Otherwise, they participate to the circadian rhythm. Corticoids act through two types of receptors: the glucocorticoid receptors (GR) and the mineralocorticoid receptors (MR). Red arrows indicate a stimulating input while purple lines indicate an inhibiting input. The CAR is the Cortisol Awakening Response.

mother and pups is modified by the experimenter. In rhesus macaques, the models used do not obey to a generally accepted protocol as it is in rodents. Thus, the protocols are very different. Some try repeated MS similar to those used in rodents [12,13], but most use whether nursery-reared rhesus macaques versus mother-reared [14,15] or peer-reared without their mother versus mother-reared [16]. Consequently, it is interesting to notice that each variation of protocol might have very distinct effects on the HPA axis and aggression.

What are the consequences of the ELS on the child's HPA axis? How is the HPA axis altered in the adult who experienced an ELS?

What are the consequences of MS on the HPA development?

In rodents, repeated MS made during the SHRP disrupts it. The HPA axis of pups which would normally underreact to any stressor is hyperactivated in response to the maternal absence (Table 1). As the SHRP is a critical period for a good maturation of the HPA axis, this implies long-lasting changes in its components. The most important change observed does not affect directly the HPA axis but the hippocampus which is essential for a negative feedback of the axis. It is still developing during the period of MS [4]. Many studies in rodents report that MS during the SHRP as low-caring mothers induce a methylation of the Glucocorticoid Receptor (GR) promoter in the exon 1_7 in the hippocampus [4,7,17–19]. This leads to low levels of expression of the GR in adulthood. Interestingly, in humans also, child neglect [17], child abuse [20] and prenatal maternal depression [21] are associated with a methylation of the exon 1_F of the GR promoter in the hippocampus. The exon 1_F is the homologous of the rodent exon 1_7. ELS are also often related to smaller hippocampus volume in rodents as in humans [22] and to problems in memory related to hippocampal dysfunction [23]. Lajud *et al.* [24] also showed that MS reduces neurogenesis in the hippocampus during the SHRP. Daniels *et al.* [25] have shown that at PND21, Sprague Dawley rats have no increase on the methylation of the exon 1_7 after MS. This might be due to the use of a different strain of rats in front of most studies which use whether Long Evans or Wistar rats or to the fact that at PND21, rats are still young and that the changes might occur lately at adulthood, as most studies of GR promoter are made later on. One last possibility may also rely on the fact that, as it is a repeated MS and not a definitive one, the dam may compensate the absence of her pups by over-caring for them when they are present [26]. Weaver [18] describes more precisely what could be

Table 1 : Consequences of the MS on the basal and on the stress-induced HPA axis activity.

	Basal HPA axis activity				Stress-induced HPA axis activity			
	Males		Females		Males		Females	
	young	adult	young	adult	young	adult	young	adult
Rats	AVP+[50]/~[50], GC~[5,24], GRh~[25]	CRH~[1,4], AVP+[50]/~[57], ACTH~[51], GC+[24,58]/~[1,51]	ND	CRH+[19]/~, GC+[19], GRh-[19]	AVP+[50], GC+[5,25]	CRH+[1]/~[28], AVP+[57]/-[28], ACTH+[4,51], GC+[1,4,24,51], GRh-[4]	ND	CRH+[28], AVP~[28]
HPA axis	~	+/~		+	+	+		+/~
Mice	ND	AVP+[29], GC+/~[46,49]	ND	AVP~[29]	ND	AVP+[29], GC+[49]/~[33,46]	ND	AVP~[29], GC+[33]/~[33]
HPA axis		+		ND		+		+/~
Rhesus	ND	CRH+[16], ACTH~[16]/-[16], GC+[16]/~[16]	ND	ND	GC~[13,47]	ND	GC+[13]/~[47]	ND
HPA axis		+			~		+/~	
Humans	ND	ACTH~[30], GC+[34]/~[30], GRh-[17]	ND	ACTH+[30], GC+[30]	ND	ACTH+[30], GC+[30]	ND	ACTH~[30], GC~[30]
HPA axis		+/~		+		+		~

ND is for No Data found. + is for an increase of HPA axis activity after MS in front of the control. ~ stands when there is no significant difference with control. - is for a decrease of the HPA axis activity after a MS. Each component of the HPA axis was observed: CRH and AVP released by the PVN, CRHR in the pituitary gland, ACTH and GC released in the blood, MC2R in the adrenal cortex, GR and MR in the hippocampus (GRh), the PVN and the pituitary. Unfortunately, many aspects of the axis have been ignored by the studies or have been observed in a non sex-specific manner, so that they couldn't be added to the table. Rodents data provided corresponds to experiments with non-handled pups or animal facility rearing pups as a control. Young is the period until weaning (≤PND21 in rodents, ≤10-14 months in rhesus macaques, ≤18-21 years old in humans). Adulthood is generally observed from PND60 and on in rodents, 5 years old and on in primates and at about 25 years old and on in humans. The numbers correspond to bibliographic references.

the mechanisms linking maternal care and epigenetic modifications of the GR exon. Interestingly, Huot *et al.* showed in 2004 [27] that, if the dam was set with another litter during the MS, the effects of the MS on the HPA axis of the pups seemed to be reversed. Sadly, there have been no further research to understand how the maternal behavior was affected by MS and how it could explain the consequences of MS in pups.

All studies agree in underlying that an ELS, here MS, induces alterations in the development of the hippocampus which is essential for the negative feedback of the HPA axis.

What are the consequences of MS on the adult HPA?

There are two principal aspects of the adult HPA which can be affected: the basal activity (circadian rhythm) (Figure 1.C) and the stress-induced activity (Figure 1.B). It appears that MS might affect both aspects on most of the models studied, although there is still much discussion.

In rodents, most of the studies show that MS induces a basal and a stress-induced hyperactivation of the HPA axis, both in male and female adults (Table 1). Nevertheless, some studies also suggest that MS induces no differences of basal nor stress-induced HPA axis activation or even a reduced HPA axis in males [28]. In front of the huge number of studies underlying the hyperactivation of the HPA axis in rodents after MS, it is hard to believe that MS won't induce any effect, although differences in genotypes or in protocols might justify such differences. As shown in Table 1, sometimes the same studies provide different results. This is generally attributed to differences in genotypes, especially in rhesus monkeys [15,16]. Furthermore, many studies do not separate males and females, although there is evidence that the effects of MS are sex-specific in all species (Table 1, [13,28–30]). Others do not provide the age of the animal when the measures are done, although it is known that age is an important factor in HPA axis functioning in Mammals. Especially in males, basal GCs increase with age [31,32]. In addition to that, in females, the HPA axis activity changes with the estrous cycle (Box 1). MS effects may be visible only at a certain period [33], what makes studies in females far more complicated.

In rhesus monkeys, Chen *et al.* [16] also proved that there might be an increase of basal CRH and GC secretion, in adult males peer-reared, following a definitive MS just after birth, but the increase in GC depends on the genotype.

In humans, the studies are consistent with these observations in animals, pinpointing that an early parental loss induces a higher cortisol awakening response (CAR) [34] and a higher response to the Dexamethasone/CRH test [35]. Although, in humans also, some studies even show that the CAR is reduced after an ELS [36]. However, the results in humans must be nuanced as the CAR is subjected to many criticisms (Box 1) and as the studies do not always separate the genders [35,36].

Consequently, early MS seems to induce a global basal and stress-induced hyperactivation of the HPA axis in adult men. In women, it might also be the case, but further studies should be done, taking into account the menstrual cycle.

Box 1. Glucocorticoids measurement

Many methods are used to measure GCs:

- hair cortisol. This measurement gives the mean of cortisol secretion for a period going from weeks to months. It is not informative on the circadian secretion or the stress-induced secretion and, in humans, the action of water and shampoo is reported to decrease the hair cortisol concentration [52] so that it is not precise at all.
- urine and faeces cortisol. The cortisol measured is a mean of the cortisol excreted some hours before. This measure is quite complicated as cortisol is often conjugated with other molecules [48].
- salivary cortisol. It is rather more precise, but neither the delay between the adrenal secretion and the presence of cortisol in the saliva nor the influence of food are very well known.
- plasma GCs. It is the most accurate technique as it gives the effective concentration in GCs in the blood.
- the CAR = the cortisol awakening response. It is measured with plasma cortisol or salivary cortisol. It lasts until 1 hour after awakening. There are many criticisms of this measurement: in women, it depends of the menstrual cycle (elevation during ovulation) [53] and pregnancy (increase during pregnancy) [54]. Generally, it is also supposed to depend on the hour of awakening [55]. There is also criticism against the fact that the measures are made with 15 to 30 minutes of delay while the delay should be of 10 minutes maximum [56].

In rodents, generally, only plasma blood measure is used as it seems to be the most accurate of all techniques. In humans, mostly salivary cortisol is used as it is the most accurate of the non-invasive techniques. In primates, nearly all of these techniques are used.

How do those ELS-induced modifications of the HPA axis impact on aggression?

How is the HPA axis connected with aggression?

A big problem of studies concerning the HPA axis and aggression is that they poorly investigate on the causal relationship of those two aspects. They generally only give correlation factors. However, some say that the decision of aggressive behavior or non-aggressive behavior in front of a conspecific is determined by the testosterone/GC ratio [37]. A high

ratio would make the balance tilt to aggression. This would in part explain the predominance of aggression in males in front of females. Some pinpoint also that a stress mediated by the PVN activation could inhibit the aggression in rodents [38]. In both cases, hyperactivating the HPA axis would thus reduce aggressiveness. Nevertheless, it looks more complicated as the injection of cortisol in humans seems to increase aggressiveness in women but not in men [39]. Thus, it underlies the necessity to study the modifications induced by an ELS specifically in each gender. Furthermore, basal level of GC seems important in relation with different types of arousal-related aggression (impulsivity for hyperarousal and GC deficient for hypoarousal) [40].

How each type of aggression might be affected by ELS and ELS-induced HPA axis modifications?

There is clearly a need of experiments in the field. Despite this, using the few studies which have been made and knowing how the HPA axis can be altered by an ELS might help us to understand how the different kinds of aggression can be affected by MS.

Females, in rodents, are generally aggressive only in the frame of maternal aggression. That means that only lactating females are concerned. Yet, we have seen that in female rats and mice, the HPA axis seems equally or more activated basally and after a stress after an early MS (Table 1). The studies which have focused on understanding maternal aggression suggest that CRH, AVP, ACTH, CRH as well as GCs inhibit maternal aggression [41–43]. Thus, MS, by increasing the stress-induced HPA axis tone, might reduce the emergency of maternal aggression. Nevertheless, further investigations are needed to verify whether the increased HPA axis tone due to MS is maintained during lactation. In rats, maternal aggression is indeed reduced after MS [1]. On the contrary, in mice, Veenema *et al.* [29] showed that adult females lactating after having been submitted to a MS had no increase of AVP in front of controls, but showed higher maternal aggression. The differences observed within rats and mice (Table 2) make it very difficult to draw any general conclusion on the consequences of MS on maternal aggression, as the mechanisms might be different. Furthermore, we know that in primates, on the contrary to rodents, females can display more kinds of aggression than the maternal one [15]. In addition to that, AVP, a component of the HPA axis, promotes maternal aggression when it is injected in the central amygdala, but not in the PVN [44]. The interactions of the HPA axis with the other areas of the brain have to be taken into account in future studies.

In humans, rhesus monkeys and rodents, MS seems to induce a higher HPA axis tone in males, both basally and after a stress (Table 1). Thus, we might expect less aggressiveness in males after early MS. In rodents, aggression is tested with the resident-intruder (RI) test. The resident-intruder (RI) test consists in putting a male in a cage with a female for quite a long time so as to create a sensation of residency. Then the female is retired before introducing a smaller intruder male. The resident generally attacks the intruder so as to protect his territory. This aggression is usually reported as an offensive aggression by the resident. In mice, Veenema *et al.* [29] showed indeed that the resident MS mice were less aggressive in the RI test than the non-MS controls. Surprisingly, male rats and rhesus monkeys appeared, on the contrary, whether more aggressive or equally aggressive after a MS (Table 2) in function of their genotype [15,16]. Thus, it seems that species and genetic particularities should also be taken into account for all kinds of aggression.

Defensive aggression is linked to an attack whether by a conspecific or by a predator. Thus, it is legitimate to think that it is linked to an activated HPA axis. Ebner *et al.* [45] showed that male intruders always show an increase in ACTH when set in the RI test. The most aggressive intruders are those who have a peak of AVP while the frightened ones are those with a decrease in AVP. Thus, it is tempting to hypothesize that defensive aggression may be linked to a specific activation of the HPA axis, especially to a raise in AVP. Thus, MS might stimulate defensive aggression.

Conclusion

The studies have shown that a MS generally induces a basal and a stress-induced hyperactivity of the HPA axis in males and eventually in females. Thus, this might reduce maternal aggression in rodents and intermale offensive aggression in rodents and primates. However, many components are involved in the aggression and looking only at the alterations of the HPA axis cannot fully explain the modulation of aggression after a MS. Much work remains to be done

Table 2 : Possible or effective consequences of early MS on HPA axis and adult aggression.

Species	Adult HPA axis stress-induced	Maternal aggression	Male offensive aggression	Defensive aggression
Rats	+m/+f	-[1]	+[1,57]	+?
Mice	+m/+~f	+[29]	-[29]	+?
Rhesus	(nd)m/(nd)f	nd	+[1,15,16]/~[15,16]	+?
Humans	+m/~f	nd	nd	+?

nd means not determined. + is for an increase of HPA axis activity for MS subjects in front of controls. ~ stands when there is no significant difference with control. - is for a decrease. ? is for the hypothesized changes given the data we have by now. m is for males and f for females. The numbers correspond to bibliographic references.

in the field: firstly by looking more scrupulously at the causal links between the HPA axis and aggression, secondly by studying the components of the HPA axis which were ignored by most studies (MC2R concentration in the adrenal cortex or CRHR in the pituitary gland, see table 1) and thirdly by leading more studies in primates.

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- • of special interest
- •• of outstanding interest

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