Chapter 9
Genetic and Epigenetic Determinants of Aggression

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Abbreviations

5-HT-R	Serotonin receptor
5-HTT	Serotonin transporter
ACTH	Adrenocorticotropin
ADX	Adrenalectomy
ANP	Atrial natriuretic peptide
AR	Androgen receptor
AVP	Arginine vasopressin
BDNF	Brain-derived neurotrophic factor
BNST	Bed nucleus of stria terminalis
CaMK	Calcium/calmodulin-dependent kinase
CeA	Central amygdala
CNS	Central nervous system
COMT	Catechol-*O*-methyltransferase
CpG	Cytosine–guanine dinucleotide
CRH	Corticotropin-releasing hormone
D2-R	Dopamine D2-receptor
DBH	Dopamine beta-hydroxylase
DNMT	DNA methyltransferase
ER	Estrogen receptor
ERα	Estrogen receptor-α
GABA	Gamma-aminobutyric acid
GR	Glucocorticoid receptor

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HAA	Hypothalamic attack area
HAT	Histone acetyltransferase
HDAC	Histone deacetylase
HPA axis	Hypothalamo–pituitary–adrenocortical axis
IL-6	Interleukin-6
KO	Knockout
L	Long variant of the 5-HTT
MAO	Monoamine oxidase
MeA	Medial amygdala
met	Methionine
MPOA	Medial preoptic area
MTHFR	Methylenetetrahydrofolate reductase
NA	Noradrenaline
NCAM	Neural cell adhesion molecule
NGF	Nerve growth factor
NK1	Neurokinin1, the receptor for substance P
NO	Nitric oxide
NOS	Nitric oxide synthase
OT	Oxytocin
PAG	Periaqueductal gray
PFC	Prefrontal cortex
POMC	Proopiomelanocortin
PVN	Nucleus paraventricularis hypothalami
S	Short variant of the 5-HTT
sc	Subcutaneous
SER	Serotonin
SON	Supraoptic nucleus
TGFα	Transforming growth factor-α
TH	Tryptophan hydroxylase
V_{1a}-R	Vasopressin V_{1a} receptor
val	Valine
VMH	Ventromedial nucleus of the hypothalamus
VPA	Valproate

9.1 Introduction

The history of genetics started with the work of Gregor Johann Mendel on pea plants, published in 1866 (Mendel 1866). Genetics deals principally with the molecular structure and function of genes, the genetic codes. However, there are heritable changes not dependent on the genomic sequence. For this kind of programming, Waddington introduced the term epigenetic in the 1940s (Waddington 1942). In the last few decades, a lot of knowledge accumulated about epigenetic modifications during development and in cancer formation; however, little is known about the role

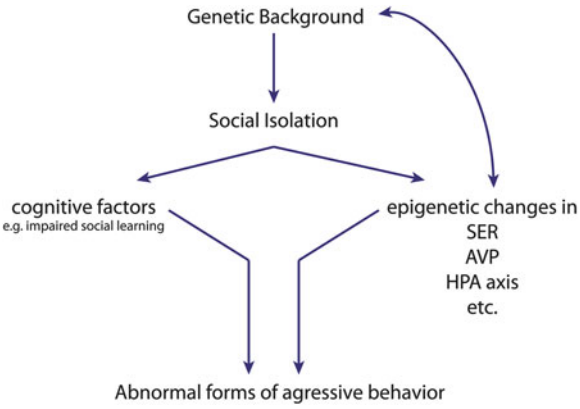

Fig. 9.1 Schematic diagram of the interaction of several factors, leading to development of pathological form of aggression. *SER* serotonin; *AVP* arginine vasopressin; *HPA axis* hypothalamo–pituitary–adrenocortical axis

of epigenetic changes in mature cells. At the moment, there is not too much direct evidence available on the connection between aggression and genetic, even more epigenetic modification. However, several facts suggest these interactions (Fig. 9.1). For example, low glucocorticoid level enhances aggression only after long-term exposure, e.g., through removal of the adrenal gland (Halasz et al. 2002), but not after an acute decrease, e.g., through metyrapone treatment (Mikics et al. 2004), raising the possibility for the development of epigenetic changes. Moreover, another model of pathologic aggression, the social isolation, is a widely used inducer of schizophrenia-like symptoms, which is—according to some theories—an epigenetic disease (Graff and Mansuy 2009). In the following, we try to summarize the present knowledge about brain areas and molecules involved in aggression, as possible targets of genetic as well as epigenetic regulation.

9.2 Why Aggression Is Important?

Every year, more than 700,000 people worldwide die because of assault (Bartolomeos et al. 2007), and many more become victims of aggressive behavior including domestic violence, terrorism, and hooliganism or get physically or psychologically injured. Besides the suffering of affected persons and their families, a large financial burden for society emerges (Neumann et al. 2010).

On the other hand, aggression is expressed by virtually all mammalian species and is of vital importance for the survival of the individual. An animal defending itself against a predator becomes aggressive in order to survive and to ensure the survival of its offspring (Gregg and Siegel 2001). Aggression against conspecifics serves to establish a dominance hierarchy for better supply of food, territory, and mating. Because winners in agonistic battles are often thought to be dominant (Bjorkqvist 2001) and aggressive behavior is often manifested in the process of hierarchy formation (de Almeida et al. 2005), many scientists equate aggressiveness with dominance. However, the dominant ones are not always the most aggressive animals in a population (Sapolsky 2005).

So, aggression is not a psychological disorder per se, but is among the symptoms of more complex psychological disorders (Vitiello et al. 1990; Scarpa and Raine 1997; Meloy 2006). It is often associated with schizophrenia, suicidal depression, and cluster B personality disorders, attention deficit/hyperactivity disorder (ADHD), which are characterized by a psychopathological complex of attentional problems, motor overactivity, and impulsivity, which is per se closely linked to behavioral problems (Retz and Rosler 2009). In addition, these disorders start early in life and, therefore, are suggested to have high impact of an individual's socialization. In fact, deficits in social behavior leading to excessive aggression may develop as a consequence of disturbed emotional regulation (Davidson et al. 2000). Accordingly, a better understanding of the link between social behaviors and emotional regulation and their neurobiological underpinnings is essential to improve the treatment of many psychopathologies (Neumann et al. 2010). When aggression occurs out of context, aggressive behaviors can become inappropriate or pathological (Veenema 2009). Interestingly, laboratory research on aggression largely ignored the existence of pathological forms of aggression and focused mainly on the mechanisms underlying natural aggression.

9.3 Models of Abnormal (Pathological) Forms of Aggression

There is no doubt that the research has to focus on pathological aggression instead of normally occurring aggressive contact during predation or defense (Blair 2001). In social species, aggression is a ritualized behavior. Therefore, it is signaled in advance to offer the weakest one the possibility to withdraw and serves for establishing a stable dominance hierarchy (Veenema 2009). It was suggested that animal aggression can be considered abnormal, if there was a mismatch between provocation and response, i.e., the aggressive response surpassed species-typical levels (de Almeida and Miczek 2002; Miczek et al. 2002); if attacks were targeted on inappropriate partners, e.g., females (de Boer et al. 2003; Natarajan et al. 2009) or inappropriate body parts, i.e., those prone to serious injury like the head, throat, and belly (Haller et al. 2001, 2005a; Haller and Kruk 2006); if attacks were not signaled by threats; or if the submissive signals of opponents were ignored (Haller et al. 2001; de Boer et al. 2003; Haller and Kruk 2006; Natarajan et al. 2009). In general, these criteria are similar to particularities of human aggressiveness that are expressed in certain aggression-related psychopathologies (Haller et al. 2005a; Haller and Kruk 2006). Four laboratory models of abnormal aggression were developed so far.

Genetic models make use of mice selected for high aggressiveness, rats selected for low anxiety, or selected subpopulations of feral rats, where abnormal features of aggression could be observed (de Boer et al. 2003; Natarajan et al. 2009; Neumann et al. 2010).

The escalated aggression model involves aggressiveness that surpasses species-typical levels and is induced by frustration or provocation (de Almeida and Miczek 2002; Miczek et al. 2002, 2004). This model is based on the attack priming phenomenon discovered by Potegal (1992).

Based upon the development of abnormal attack targeting, i.e., the ratio of attacks aimed at vulnerable targets, e.g., head, throat, and belly (Haller et al. 2001), the hypoarousal model was introduced. It involves the chronic limitation of glucocorticoid secretion, which mimics the low glucocorticoid levels seen in violent, antisocially disordered people (Haller et al. 2001; Haller and Kruk 2006). When the glucocorticoid secretion was stabilized at a low level by adrenalectomy with subcutaneous glucocorticoid pellets (ADX), a change in attack targeting can be detected (Haller et al. 2001). While control rats targeted biting attacks towards less vulnerable dorsal parts of the opponent's body, ADX rats attacked the head frequently. This was accompanied by autonomic hypoarousal and social deficit as well (Haller et al. 2004). It was also shown that the neural background and pharmacological responsiveness of attacks performed by such rats are markedly altered (Halasz et al. 2002). This suggests that mechanisms of "normal" and pathologic aggression could be different.

Aggressive behavior was increased on the long run by a variety of early adverse experiences, e.g., maternal separation (Suomi 1997; Veenema et al. 2006, 2007a) or early defeat (Delville et al. 1998; Wommack et al. 2003). However, the pathological feature of early social isolation-induced aggression was confirmed just recently (Toth et al. 2011). Namely, social isolation from weaning to the ages of 80 days not only increases the level of aggressiveness but results in abnormal attack patterns and deficits in social communication. So it models the aggression-related problems resulting from early social neglect in humans (Toth et al. 2008). Recently, it was also shown that the aggression-induced glucocorticoid and autonomic stress responses are substantially increased in these rats, suggesting that social isolation from weaning may be used as a model of aggression-related psychopathologies associated with hyperarousal (Toth et al. 2011).

These models underline that stress, thereby the hypothalamo–pituitary–adrenocortical (HPA) axis, plays a key role in the regulation of aggression.

9.4 Brain Areas Involved in Aggression

The main neuronal axis for controlling normal aggression is the medial amygdala (MeA)–hypothalamic attack area (HAA)–periaqueductal gray (PAG) axis, which is modulated by other areas such as the prefrontal cortex (PFC), lateral septum, other amygdaloid nuclei, and the brain stem monoaminergic nuclei (Gregg and Siegel 2001) (Fig. 9.2). The dysfunction of neural circuits responsible for emotional control was shown to represent an etiological factor of aggression and could be target areas for epigenetic modifications.

The so-called HAA is the only brain region from where attacks can be reliably elicited by electrical or optogenetic stimulation in all the investigated species, including cat, rat, and mouse (Lammers et al. 1988; Lin et al. 2011). This functional brain region is located in the mediobasal portion of the hypothalamus and partly overlaps with the anterior hypothalamic area, tuber cinereum area, and the ventromedial hypothalamic nucleus (Lammers et al. 1988; Hrabovszky et al. 2005).

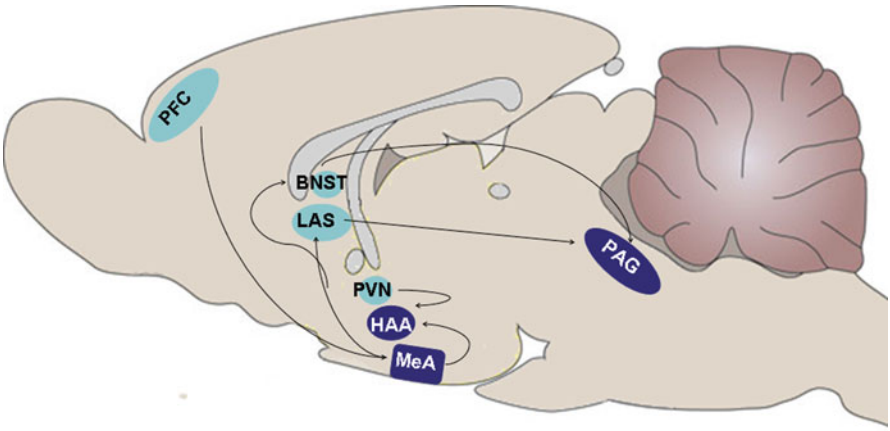

Fig. 9.2 Most important brain areas involved in aggression and their connections. *MeA* medial amygdala; *HAA* hypothalamic attack area; *PAG* periaqueductal gray; *PFC* prefrontal cortex; *LAS* lateral septum; *BNST* bed nucleus of stria terminalis; *PVN* paraventricularis nucleus of hypothalamus

The HAA stimulates the dorsal PAG via glutamatergic projections (Fuchs et al. 1985a, b). From this latter region, aggressive behavior can be elicited by electrical stimulation in the cat (Shaikh et al. 1987), but not in the rat, but still, it is an important locus for aggression control even in the rat (Lonstein and Stern 1998; Tulogdi et al. 2010).

MeA regulates the activity of the HAA through substance P neurotransmission, acting on neurokinin receptors (Shaikh et al. 1993). Antagonizing neurokinin 1 receptors systemically or by eliminating the neurons that express this receptor from the HAA results in a marked attenuation of aggressive attacks, especially that of violent attacks (Halasz et al. 2008, 2009). Moreover, stimulation of the MeA promotes intraspecific aggression, and lesion of this region attenuates aggressive behavior (Brutus et al. 1986; Vochteloo and Koolhaas 1987). Importantly, surgical lesion of the amygdala and/or the hypothalamus is a very effective method for taming even extremely violent psychiatric patients (Ramamurthi 1988; Sano and Mayanagi 1988). Structural and functional alterations of the amygdala were repeatedly shown in violent patients using different brain imaging techniques, e.g., reduced volume (Zhang et al. 2011) or asymmetrical activation pattern (Raine et al. 1997).

Together with the amygdala, the subregions of the PFC are the most frequently implicated brain regions in normal and abnormal human aggression. Some authors claim that violence is a consequence of the dysfunction of these brain regions, i.e., brain regions relevant for emotion regulation (Davidson et al. 2000). Watching angry facial expressions or thinking about personalized situations that induce anger was associated with enhanced activity in the orbitofrontal and anterior cingulate cortices (Blair et al. 1999; Dougherty et al. 1999). Impulsive personality-disordered people showed blunted metabolic responses to a serotonergic challenge in the orbitofrontal, ventromedial prefrontal, and cingulate cortices (Siever et al. 1999).

PFC lesions often lead to aggressive behavior in humans, as shown, for example, in Vietnam veterans (Grafman et al. 1996). Similar results were found in rhesus monkeys (Butter and Snyder 1972) and laboratory rodents (Rudebeck et al. 2007). These findings suggest that PFC provides the main inhibitory function over aggression. This function could be executed via direct projections to the MeA and the HAA (Toth et al. 2010).

Another important inhibitory region is the lateral septum, as lesioning or blocking this region enhances aggressiveness (Harrell and Balagura 1975; Albert and Wong 1978). The bed nucleus of stria terminalis (BNST) plays also a significant role in the expression of social preferences, affiliation, and aggression in rats, mice, and hamsters (Newman 1999; Rasia-Filho et al. 2000; Ferguson et al. 2001) and prairie voles (Wang and De Vries 1993; De Vries and Villalba 1997; Wang et al. 1997), suggesting that this region of the brain has a similar function in both highly social and less social species. The BNST is part of the accessory olfactory system, also known as the vomeronasal system, which is crucial for the detection of pheromones and influences several aspects of reproduction, including sex discrimination, attraction, and mate recognition (Wysocki 1979). In addition to having projections to the medial preoptic area (MPOA) and lateral septum, the BNST also projects to the vasopressin (arginine vasopressin, AVP) and oxytocin (OT) neurons of the nucleus paraventricularis hypothalami (PVN) and supraoptic nucleus (SON) (Sawchenko and Swanson 1983), suggesting that it can also regulate the production or release of these neuropeptides. Moreover, BNST sends dense projections to the HAA (Toth et al. 2010).

Recent data suggest that it is really important to differentiate between different forms of pathological aggression when measuring their neural background. In the hypoarousal-driven aggression, the role of the lateral hypothalamus and central amygdala increases on the expense of the roles played by the HAA and MeA (Halasz et al. 2002; Tulogdi et al. 2010). The activation patterns of the PFC (Halasz et al. 2006) and the PAG (Tulogdi et al. 2010) are also altered, while the regulatory roles of the lateral septum (Haller et al. 2006) and raphe serotonergic nuclei (Haller et al. 2005b) seem to be eliminated. Taken together, brain regions relevant for hypoarousal-driven aggression seem to modulate this form of violent behavior (Gregg and Siegel 2001; Halasz et al. 2002; Tulogdi et al. 2010). In contrast, the hyperarousal-driven aggression of socially isolated rats seems to be regulated by the hyperfunctioning of the above mentioned brain regions relevant for normal aggressive behavior, namely, the orbitofrontal cortex, MeA, and the HAA (our unpublished data).

9.5 Molecular Mechanisms of Aggression Control

The role of neurotransmitters and their receptors in preclinical studies of aggression has guided much of the development of pharmacotherapeutic interventions during the past decades (Miczek et al. 2002). The canonical aminergic transmitters such as serotonin (SER) and dopamine are still the basis for current drug treatments of violent individuals; however, they have been complemented by a better understanding

Table 9.1 Molecules involved in aggression

Group	Molecule	Knockout	Effect of KO on aggression	Polymorphism	Epigenetic changes
Sexual steroids	Testosterone	AR	↓	AR	
	Estradiol	ERα	↓		ERα
		ERβ	↑		
Catecholamines	Serotonin	5-HT_{1A}-R	↓	TH, 5-HTT, SER receptors	5-HTT
		5-HT_{1B}-R	↑		
	Dopamine	MAO-A	↑	MAO, COMT	
	Noradrenaline			DBH	
Neuropeptides	Vasopressin	V_{1b}-R	↓	V_{1b}-R	AVP, AVP–valproate
	Oxytocin	OT	↓↑		
	Substance P	NK1-R	↓		
GABA		GAT1	↓		
Neurotrophins	NGF				NGF
	BDNF	BDNF	↑		BDNF
Endocannabinoids		CB1-R			
Stress axis					CRH, POMC, GR

AR androgen receptor; *ER* estrogen receptor; *5-HT-R* serotonin receptor; *SER* serotonin; *5-HTT* serotonin transported; *MAO* monoamine oxidase; *COMT* catechol-*O*-methyltransferase; *DBH* dopamine beta-hydroxylase; *V_{1b}-R* vasopressin 1b receptor; *AVP* vasopressin; *OT* oxytocin; *NK1-R* neurokinin 1 receptor; *GABA* gamma-aminobutyric acid; *GAT1* GABA transporter subtype 1; *NGF* nerve growth factor; *BDNF* brain-derived growth factor; *CB1-R* cannabinoid receptor 1; *CRH* corticotropin-releasing hormone; *POMC* proopiomelanocortin; *GR* glucocorticoid receptor

of modulatory influences by gamma-aminobutyric acid (GABA) as well as neuropeptides (Miczek et al. 2004; Miczek and Fish 2005). In Table 9.1, we summarized the molecules, the effect of knocking out a gene in the system and the available data on polymorphisms and epigenetic changes related to aggressive behavior.

9.5.1 Testosterone

Among all hormones, testosterone is most consistently linked to aggressive behavior (Giammanco et al. 2005). Notably, the level of aggression in males is far higher than in females (Giammanco et al. 2005), similar to the spectrum of morphological, physiological, behavioral, and psychological differences that are determined mostly by the sex hormones. This fact has brought many researchers to the conclusion that the determinants of aggression are androgens. It is supported by the well-documented fact that castration eliminates aggression (Nelson and Chiavegatto 2001).

There is evidence indicating a link between testosterone and antisocial behavior in humans as well (Dabbs and Hargrove 1997). Many researchers believe that high correlation exists between testosterone level and dominance or — in human social interaction — status-related behaviors, too (Archer 2006). A vast number of publications indicate a high level of testosterone in dominant animals, in the winners of agonistic contests (Cavigelli and Pereira 2000; Hardy et al. 2002; Oyegbile and Marler 2005), or in the winners between competing humans (McCaul et al. 1992; Bernhardt et al. 1998; Zitzmann and Nieschlag 2001; Giammanco et al. 2005; Schultheiss et al. 2005).

On the other hand, it is known that one of the main inducers of aggressive behavior is frustration (David et al. 2004), which, in turn, may be related to emotional stress. Stress suppresses androgen synthesis in rats (Andersen et al. 2004; Hardy et al. 2005; Razzoli et al. 2006), mice (Dong et al. 2004), hamsters (Castro and Matt 1997), primates (Lado-Abeal et al. 2001), and humans (Gozes et al. 1982; Ferris and Potegal 1988; Elman et al. 2001; Pavlov et al. 2012). Such suppression to a greater or lesser extent may be caused by a variety of stressors (Andersen et al. 2004; Razzoli et al. 2006). Although aggression is commonly related to a high level of testosterone, agonistic conflict is often stressogenic for both dominants and subordinates, and stress causes the inhibition of hormonal components of the reproductive system (Chichinadze and Chichinadze 2008). Thus, testosterone is not always an inducer of aggressive behavior (Aujard and Perret 1998; Morgan et al. 2000). Indeed, an association between testosterone and aggression is weak in humans except among abusers of anabolic steroids (Zitzmann and Nieschlag 2001).

In the rodent brain, aromatase converts testosterone into estradiol that is responsible for masculinization of the brain and regulates aggression and infanticide through estrogen receptor-α (ERα) (Ogawa et al. 1998; Wilson 2001).

9.5.1.1 Mechanisms of Action

According to the organizing/activating model of testosterone action suggested by vom Saal (1983), androgens during the prenatal period contribute to the formation of a neuronal network, which, in the future, participates in aggressive behavior. During pubescence, this network is activated also by testosterone, and in response to properly presented stimuli, an aggressive behavior is formed (Book et al. 2001). Thus, the primary role of testosterone may be the formation of structures that generate highly aggressive responses to external stimuli. This process might involve epigenetic mechanisms (see below). Androgens seem to promote aggressiveness at the level of the lateral septum, MPOA, amygdala, and dorsal raphe nucleus (Simon et al. 1998). Imbalance in testosterone/SER and testosterone/cortisol ratios, e.g., increased testosterone levels and reduced cortisol levels, increases the propensity toward aggression because of reduced activation of the neural circuitry of impulse control and self-regulation (Pavlov et al. 2012).

9.5.2 Serotonin

Although several neurotransmitters were connected with aggression, the SER data are the most convincing (Nelson and Chiavegatto 2001). Traditionally, many studies have shown that elevated SER levels lead to decreased aggression in many different species (Chiavegatto and Nelson 2003), including humans (Coccaro et al. 1994; Unis et al. 1997). This finding has been replicated in populations of impulsive offenders, adults, and children (Brown et al. 1979; Linnoila et al. 1983). However, the identification of genes for at least 14 SER receptor proteins, variants of the synthetic and metabolic enzymes, and transporter molecules underlines the molecular diversity of the serotonergic mechanisms of action (de Almeida et al. 2005). Moreover, genetic analyses of aggressive individuals have identified several molecules that affect the SER system directly, e.g., 5-HT_{1B}-R, SER transporter, and monoamine oxidase-A (MAO-A), or, indirectly, e.g., neuropeptide Y, nitric oxide synthase (NOS), and brain-derived neurotrophic factor (BDNF) (Takahashi et al. 2011).

Pharmacological strategies of increasing SER levels, such as the use of SER precursors, SER reuptake inhibitors, in addition to the agonists of its receptor, 5-HT_{1A}-R and 5-HT_{1B}-R, are able to reduce aggressive behavior in rodents (Olivier et al. 1995; Miczek et al. 1998; Fish et al. 1999; Lyons et al. 1999; Chiavegatto et al. 2001). When activated systemically, 5-HT_{1B}-Rs appear to be essential sites for the inhibition of several types of aggressive behavior. The decrease of heightened aggression was observed in studies using mice after intraperitoneal administration of 5-HT_{1B}-R agonists such as CP-94,253, zolmitriptan, and anpirtoline (Fish et al. 1999; de Almeida et al. 2001, 2005; de Almeida and Miczek 2002). In human samples, aggressive behavior is strongly and negatively correlated with the level of the SER metabolite 5-hydroxyindoleacetic acid, measured in the cerebrospinal fluid (Virkkunen et al. 1994). Taken together, SER was suggested to inhibit aggressive behavior in animals and violent behavior in humans (Haller et al. 2005a).

The MeA–HAA–PAG axis, as well as the PFC and lateral septum, is influenced by SER coming from the brain stem raphe nuclei. The PFC, more specifically the orbitofrontal region, has been identified to be particularly important in the inhibitory control of behavior, mainly impulsive and aggressive behavior (Blair 2001; Cardinal et al. 2004; Seguin 2004; Spinella 2004; Kheramin et al. 2005). SER facilitates prefrontal inhibition, wherefore insufficient serotonergic activity can enhance aggression (Pavlov et al. 2012) and pharmacological activation of PFC 5-HT_{1A}-R and 5-HT_{1B}-R was shown to inhibit the execution of aggressive behavior (de Almeida et al. 2005). The 5-HT_{1B}-R expressed in a variety of brain regions, including the basal ganglia, PAG, hippocampus, lateral septum, and raphe nuclei, either presynaptically inhibiting SER release or as a heteroreceptor modulating the release of other neurotransmitters (Nelson and Chiavegatto 2001). Although both 5-HT_{1A}-R and 5-HT_{1B}-R control the SER tone, these two receptors probably have different contributions in particular brain areas that modulate the postsynaptic SER inhibitory effects on aggression. Drugs that target the 5-HT_{1C}-R, 5-HT_2-R, or 5-HT_3-R sites have generally not influenced aggression (Valzelli 1984; Simon et al. 1998).

It can be anticipated that currently developed tools for targeting the specific subtypes of SER receptors will offer new therapeutic options for reducing aggressive behavior, and the 5-HT_{1B}-R appears to be a promising target (Miczek et al. 2007). The modulation of GABA and $GABA_A$ receptors by SER in corticolimbic neurons promises to be particularly relevant for specific forms of escalated aggressive behavior such as alcohol-heightened aggression (Takahashi et al. 2010).

9.5.3 Other Catecholamines

9.5.3.1 Dopamine

Several studies indicate that the mesocorticolimbic dopamine (DA) system is involved in aggressive acts (Mos and van Valkenburg 1979; Louilot et al. 1986; Haney et al. 1990; Puglisi-Allegra and Cabib 1990; van Erp and Miczek 2000; Ferrari et al. 2003; de Almeida et al. 2005). Pharmacologically induced DA increases are associated with increased aggressive behavior (Senault 1968, 1971; Hasselager et al. 1972; Miczek 1974; Puech et al. 1974; Crawley et al. 1975; Ray et al. 1983).

In connection with these studies, in human aggression, the most frequent and enduring pharmacotherapeutic interventions rely on compounds that act as dopaminergic antagonists (Yudofsky et al. 1984; Gualtieri and Schroeder 1990; McDougle et al. 1998). For example, the DA D2-receptor (D2-R) antagonist haloperidol has been used for decades to treat aggressive behavior of psychotic patients (Glazer and Dickson 1998; Fitzgerald 1999). This drug also decreases violent outbursts in individuals with dementia and individuals with borderline personality disorder as well as in children and adolescents, who exhibit conduct disorder and aggression (Pies and Popli 1995; Beauchaine et al. 2000; Challman and Lipsky 2000; Kennedy et al. 2001; Diederich et al. 2003; Masi 2004). The decrease in aggression is closely linked to the sedative effects. However, the more recently developed atypical neuroleptics which are considerably less sedative are more effective and have more specific antiaggressive effects. Moreover, D2-R and D4-R gene variants and interaction between them are associated with conduct disorder and antisocial behavior (Beaver et al. 2007; Congdon et al. 2008). It was also shown that D2-Rs in the region of the MPOA area and anterior hypothalamus facilitate affective defense behavior in the cat (Sweidan et al. 1991). Aggression was decreased, and hypothalamic SER and noradrenaline (NA) were increased in birds from all strains treated with D2-R antagonist (Dennis and Cheng 2011).

The neurochemical studies link elevated DA and its metabolites in PFC and nucleus accumbens not only to the initiation of attacks and threats and its consequences but also to the defensive and submissive responses in reaction to being attacked (Puglisi-Allegra and Cabib 1990; Tidey and Miczek 1996). The lack of differentiation in mesocorticolimbic dopamine activity between attack and defensive behavior suggests that neuroleptic compounds with a high affinity for D2-R would not be specific antiaggressive treatments.

9.5.3.2 Noradrenaline

NA affects aggression on three different levels: the hormonal level, the sympathetic autonomous nervous system, and central nervous system (CNS) (Haller et al. 1998). Hormonal catecholamines (adrenaline and NA) appear to be involved in metabolic preparations for the prospective fight; the sympathetic system ensures appropriate cardiovascular reaction, while the CNS noradrenergic system prepares the animal for the prospective fight. Indirect CNS effects include the shift of attention towards socially relevant stimuli, the enhancement of olfaction (a major source of information in rodents), the decrease in pain sensitivity, and the enhancement of memory (an aggressive encounter is very relevant for the future of the animal). Concerning more aggression-specific effects, one may notice that a slight activation of the central noradrenergic system stimulates aggression, while a strong activation decreases fight readiness. This biphasic effect may allow the animal to engage or to avoid the conflict, depending on the strength of social challenge. Different receptor subtypes may influence different aspect of behavior. Namely, neurons bearing postsynaptic alpha2-adrenoceptors are responsible for the start and maintenance of aggression, while a situation-dependent fine-tuning is realized through neurons equipped with beta-adrenoceptors. The latter phenomenon may be dependent on a NA-induced glucocorticoid secretion.

9.5.3.3 Catabolism

Two major enzymes are responsible for catecholamine (SER, DA, and NA) catabolism in the brain: catechol-*O*-methyltransferase (COMT) and monoamine oxidase-A (MAO-A) (Shih et al. 1999). If aggressive behavior is enhanced by catecholaminergic activity, then the lower activity of COMT and MAO-A (resulting in a slower inactivation of catecholamines) should indirectly enhance aggression. This prediction has been supported by most, but not all, observations in rodents and humans. Male mice whose COMT or MAO-A genes are deleted show elevated aggression (Cases et al. 1995; Gogos et al. 1998). On the contrary, inhibition of MAO-A correlates with reduced aggression in isolated male mice (Florvall et al. 1978) and footshock-induced aggression (Datla and Bhattacharya 1990), probably as a result of increased SER levels. The COMT gene has been associated with an increased aggressive behavior, at least in several samples of psychiatric patients (Volavka et al. 2004). There is an association between MAO-A and hyperarousal-driven aggression, too (Meyer-Lindenberg et al. 2006).

9.5.4 Neuropeptides

9.5.4.1 Vasopressin

AVP is another key hormone—besides sexual steroids—that plays a crucial role in aggression (Delville et al. 1996; Bester-Meredith et al. 1999) and other social behaviors (Albers and Bamshad 1998; Ferris 2000). Our previous studies implicated that

one of the most important central regulators of the stress axis is also the AVP (Zelena et al. 2009). Recently, the involvement of AVP in "normal" aggressive behavior comes to the front (Neumann et al. 2010). In pupfish, a correlation was found between vasotocin (the fish equivalent of AVP) and aggressive behavior, too (Lema 2006).

There are some putative sites where AVP might influence "normal" aggressive behavior. In male Syrian hamsters, AVP injected into the HAA stimulated aggression, while injection of a V_{1a} receptor (-R) antagonist inhibited the behavior (Ferris and Potegal 1988), although V_{1b} -Rs might be also involved (Blanchard et al. 2005). In mice, the BNST may increase AVP-Fos colocalization selectively in response to affiliation-related stimuli (Ho et al. 2010). In rats, AVP release within the lateral septum correlates positively with intermale aggression (Beiderbeck et al. 2007; Veenema and Neumann 2007; Veenema et al. 2007b), while a specific V_{1a}-R antagonist prevents an increase in aggression during a second contact (Veenema et al. 2010). The V_{1a}-R binding in the lateral septum positively correlated with maternal aggression (Caughey et al. 2011). Moreover, injection of a selective V_{1a} receptor antagonist into the CeA reduced maternal aggression in dams with high anxiety-related behavior, whereas synthetic AVP increased the low level of aggression in rats with low anxiety-related behavior. Selective aggression in pair-bonded male prairie voles was associated with increased release of AVP in the anterior hypothalamus (Gobrogge et al. 2009). Pharmacological activation of the V_{1a} receptors in the anterior hypothalamus was induced, whereas V_{1a} blockade diminished selective aggression in pair-bonded males. As this brain area does not get vasopressinergic innervation, the origin of AVP is questionable. We can hypothesize that somatic–dendritic release of AVP from the PVN might reach this area (Engelmann et al. 2004), therefore AVP might be one of the mechanisms that connect the stress response with aggressiveness.

The extrahypothalamic AVP system in the rat brain is highly sexually dimorphic and steroid responsive (De Vries et al. 1994). Adult male rats have twice more AVP-expressing cells in the BNST compared with females (Van Leeuwen et al. 1985; Miller et al. 1989b). AVP expression within this area is dependent upon gonadal hormones, as castration results in a significant decrease in AVP mRNA and protein expression, and testosterone replacement restores AVP expression (De Vries et al. 1985; Miller et al. 1989a; Brot et al. 1993). It is essentially estradiol, a metabolite of testosterone, that is the major factor regulating AVP expression mainly by acting upon neuronal ERα. Interestingly, castration is known to increase ERα mRNA together with a decrease in AVP (Brot et al. 1993; Handa et al. 1996).

There is an interaction between AVP and SER, too. Microinjections of AVP into the HAA in combination with 5-HT_{1A}-R or 5-HT_{1B}-R agonists revealed that only the 5-HT_{1A}-R activation inhibited AVP-facilitated aggression (Ferris et al. 1999).

9.5.4.2 Oxytocin

Oxytocin (OT) appears to act at OT receptors in the MPOA to facilitate the release of DA from neurons in the ventral tegmental nucleus, and the increased DA release then activates maternal behavior in rats (Champagne et al. 2004). OT also regulates specific forms of aggression and has differential effects depending upon the species.

OT inhibits aggressive interactions between dominant and subordinate adult female hamsters (Harmon et al. 2002). In rats, OT receptor binding positively correlated with the peak of maternal aggression, suggesting that OT may act in the lateral septum to facilitate the expression of aggressive behavior (Caughey et al. 2011).

Although many of the effects of OT are expressed primarily in females, OT also affects male behavior including social recognition (Ferguson et al. 2001), the formation of partner preferences (Cho et al. 1999), and male sexual behavior (Arletti et al. 1985; Witt 1997). In the monogamous, highly social prairie voles, a single intraperitoneal injection on the day of birth with OT or OT antagonist affected partner preference formation and aggression (Bales and Carter 2003). However, in general, OT has been shown to regulate maternal behavior (Pedersen and Prange 1979; Pedersen et al. 1982), while AVP plays a role in the expression of paternal behavior (De Vries and Villalba 1997; Bester-Meredith et al. 1999; Parker and Lee 2001). In hamsters, AVP increases aggression in males, but not in females (Cushing and Kramer 2005), and OT inhibits female aggression (Harmon et al. 2002).

Neonatal treatment with AVP increased aggression in adult male prairie voles, but not females (Stribley and Carter 1999). On the contrary, a single injection of OT on the day of birth altered the number of neurons in the PVN that expressed OT in female prairie voles, but not in males. These results support the hypothesis that while both neuropeptides may have a role in social behavior, OT may have a greater influence in the expression of prosocial behavior in females and AVP in males (Winslow and Insel 1993; De Vries and Villalba 1997; Insel et al. 1998). As the expression of OT and AVP receptors does not appear to be sexually dimorphic, other mechanisms maybe at play in establishing distinct behavioral responses to these neuropeptides.

9.5.4.3 Substance P: Neurokinin 1 Receptor

Substance P and its tachykinin NK1 receptors are highly expressed in brain regions involved in emotional control. More specifically, HAA, the only brain region in rats from which biting attacks can reliably be elicited by both electrical and neurochemical stimulation, preferentially expresses the NK1 receptors (Halasz et al. 2009). The involvement of substance P and its receptor NK1 in the induction of both defensive rage and predatory attack appears to be a consistent finding (Katsouni et al. 2009). Glucocorticoid deficiency-induced antisocial aggressiveness results from altered SER and substance P neurotransmissions (Kim and Haller 2007). Moreover, besides anxiety and depression, substance P is involved in the modulation of suicidal-related behaviors (Giegling et al. 2007).

Pharmacological studies point to a stimulatory action of substance P in aggression, as NK1 blockade lowered the development of pathologic aggression (Halasz et al. 2008). Immunohistochemical studies revealed that fos-positive, i.e., activated, neurons in the PAG of cats activated after defensive rage-inducing medial hypothalamic stimulation lie in the same region as substance-P-immunoreactive cells (Gregg and Siegel 2003). In rats, aggressive encounters activated a large number of NK1

receptor-expressing neurons in HAA as well (Halasz et al. 2008). A lesion of NK1 positive neurons through the infusion of substance-P-conjugated saporin into the HAA reduced violent attacks dramatically, whereas milder forms of aggression (soft bites and offensive threats) remained unaltered (Halasz et al. 2009).

9.5.5 Gamma-Aminobutyric Acid

Earlier postmortem studies showed that brain levels of GABA and its synthesizing enzyme, glutamic acid decarboxylase, in special brain areas are decreased in mice and rats that exhibited aggressive behavior (Clement et al. 1987; Haug et al. 1987; Guillot and Chapouthier 1998). These data have been interpreted as concordant with the proposed inhibitory role of GABA on aggression.

Indeed, several other studies supported this idea. When GABA degradation is decreased through blocking the transaminase with valproate (VPA) or through inhibiting the reuptake, aggressive behavior is diminished in mice and rats (Puglisi-Allegra et al. 1979; Puglisi-Allegra and Mandel 1980; Krsiak et al. 1981; Rodgers and Depaulis 1982). Bjork et al. 2001 found a negative correlation between plasma GABA and aggressiveness in psychiatrically healthy adults with a family history of psychiatric disorders, although it is unclear how plasma levels are related to those in neural tissue. Nevertheless, benzodiazepines by enhancing the effect of GABA on $GABA_A$ receptors reduce aggression (DiMascio 1973; Jonas et al. 1992; Cherek and Lane 2001; Friedel 2004). Therefore, psychiatric patients with violent outbursts as well as those with episodic dyscontrol syndrome are often treated with benzodiazepines (Jonas et al. 1992; Cherek and Lane 2001; Gregg and Siegel 2001; Friedel 2004).

There is abundant neurochemical and behavioral evidence that GABA and SER interact in various brain regions. For example, the raphe nuclei receive a large GABAergic input and contain many GABAergic interneurons (Harandi et al. 1987). In the raphe, between 70 and 90% of serotonergic neurons also contain a subunit of the $GABA_A$ receptor (Gao et al. 1993). One of the neurobiological mechanisms for escalated aggressive behavior may involve increased activation of $GABA_A$ receptors that are modulated by the prevailing serotonergic tone in corticolimbic projection areas (de Almeida et al. 2005).

9.5.6 Neurotrophins

Nerve growth factor (NGF) was the first discovered and so far best characterized member of the neurotrophin family, which includes BDNF and neurotrophin-3 and neurotrophin-5 (Barde 1990; Huang and Reichardt 2001).

During fighting NGF is released into the bloodstream (Aloe et al. 1986; Lakshmanan 1986, 1987; Stephani et al. 1987; Alleva and Santucci 2001; Aloe et al. 2002). Serum NGF levels reflect the individual social status: mice that

experienced repeated defeat and submissions, i.e., a subordinate status, show doubled serum NGF levels compared to attacking mice that achieved a dominant status (Maestripieri et al. 1990). Mice displaying a subordinate behavioral profile have high levels of NGF, while those displaying a dominant behavioral profile have high levels of BDNF in their hypothalamus (Fiore et al. 2003).

In the mouse, the largest amount of NGF is present in the submaxillary salivary glands (Aloe et al. 1994b). Sialoadenectomy, i.e., surgical removal of salivary glands, results in a minimal NGF increase after fighting, indicating that salivary glands are the main source of NGF in these conditions (Hendry and Iversen 1973; Aloe et al. 1986). Both the pronounced NGF increase found in subordinates, which bite very rarely, and the fact that NGF increases also in dominants, which do not receive bites by subordinates, suggest that NGF release is not due to the mechanics of biting (Maestripieri et al. 1990). However, NGF is also secreted from sources other than the salivary glands, including epithelial cells, fibroblasts, and lymphocytes, as well as activated macrophages (Gozes et al. 1982; Bandtlow et al. 1987; Lindholm et al. 1987; De Simone et al. 1990; Cirulli et al. 1998).

NGF is also present in the CNS, especially in the hypothalamus (Branchi et al. 2004). The relevance of the changes in NGF level in the hypothalamus following mouse intermale fighting, and the mechanisms involved, is however still a matter of discussion (Alleva and Aloe 1989). It was hypothesized that the rather rapid increase in the levels of brain NGF that follows a psychosocial stressful event may allow some phenomena of brain plasticity to take place in the adult animal. Indeed, NGF has been reported to regulate structural changes, such as formation of dendritic spines or collateral sprouting, ultimately altering the structure of neural connections in the mature brain (Diamond et al. 1987). Another possibility is that hypothalamic NGF may affect levels of other peptides or hormones present in this structure (Swanson and Sawchenko 1983; Albert et al. 1987). A series of interactive effects between NGF and thyroid hormones, adrenocorticotropin, and peptides have been reported (Aloe and Levi-Montalcini 1980; Otten et al. 1984; Wion et al. 1985).

NGF release is markedly triggered by psychosocial stressors (Weiss 1968; Henry et al. 1971; Axelrod and Reisine 1984; Alleva and Santucci 2001), i.e., those stressful conditions involving social interaction with conspecifics, including intermale fighting and at lower levels interfemale aggressive behavior, as well as precopula sexual arousal (Alleva et al. 1993; Alleva and Santucci 2001). Physical-stress conditions such as cold water swim, escapable or inescapable footshock, forced biting, or forced restraint exert a less pronounced effect on NGF release (Aloe et al. 1986; Alleva and Santucci 2001). Several in vivo and in vitro studies have shown that NGF also acts as a trophic and differentiative agent for the chromaffin tissue contained in the adrenal gland (Aloe and Levi-Montalcini 1979). It is has been widely reported that mouse adrenals change rather markedly and quickly following fighting behavior in males, while female adrenal morphology is more stable (Brain 1972). It therefore appeared likely that in mice, circulating NGF released by the salivary glands, regulated by social/aggressive behavior, controls adrenal morphology as well as adrenal functional status (Alleva et al. 1993). Indeed, exogenous NGF administrations markedly increase adrenal size (Aloe et al. 1986; Alleva and Santucci 2001).

9.5.7 Endocannabinoids

Taking into consideration the widespread occurrence of the endocannabinoid receptors, and the involvement of endocannabinoids in a wide range of physiological and pathological processes, one can hypothesize that the endocannabinoid system is involved in controlling aggression, too. Indeed, a diet deficient in polyunsaturated fatty acids, which might reduce endocannabinoid levels resulted in more aggressive rats (DeMar et al. 2006). Marijuana smoking increased aggressive responding for the first hour after smoking, which returned to placebo levels later in the day (Cherek et al. 1993). The effect could be dose dependent as the subjects in the low-dose condition tended to respond in a more aggressive manner than the subjects in the moderate- and high-dose conditions (Myerscough and Taylor 1985). Moreover, delta-tetrahydrocannabinol, the psychoactive component of marijuana, is also known to induce muricidal behavior in different rat strains (Bac et al. 2002).

9.5.8 Stress Axis

One of the best characterized pathologic aggression models is the hypoarousal model induced by ADX, i.e., removal of the glucocorticoids (Haller et al. 2004). Thereby, the stress axis seems to be a crucial component in the regulation of aggressive behavior.

Under the effect of acute and chronic stressful stimuli, the parvocellular neurons of the PVN release both corticotropin-releasing hormone (CRH) and AVP to the portal blood (Harbuz and Lightman 1989; Antoni 1993). In response to CRH and AVP, the synthesis of adrenocorticotropin (ACTH) from proopiomelanocortin (POMC) precursor as well as its release into the general circulation is increased. As a consequence, glucocorticoids are released from the adrenal cortex. Acute stress responses are blocked by an inhibitory feedback provided by adrenal glucocorticoids, which reduce the secretory activity of the endocrinomotor neurons of the hypothalamus and the POMC producing cells of the anterior pituitary (Kjaer et al. 1993).

9.6 Genetic Changes in Aggression

Despite the heterogeneity of definitions and classifications used and the difficulties regarding operationalization and assessment of antisocial behavior phenotypes, there is clear evidence from twin, adoption, and molecular genetic studies to support the notion that there are genetic influences on antisocial and aggressive behavior (Retz and Rosler 2009). A meta-analysis of 51 twin and adoption studies estimated moderate genetic (additive 32%, nonadditive 9%) and environmental influences (shared 16%, nonshared 43%) on antisocial behavior (Rhee and Waldman 2002). Nevertheless, aggression is highly heritable: by selective breeding, highly aggressive and virtually

nonaggressive lines can be produced in different species. Among *Drosophila melanogaster* in only ten generations of selection, the aggressive lines became markedly more aggressive than the neutral lines (Dierick and Greenspan 2006). After 21 generations, the fighting index increased more than 30-fold. Mice genetically selected for short attack latency constitute a feasible model for hypoarousal-driven aggression (Veenema et al. 2004; Haller and Kruk 2006; Vekovischeva et al. 2007; Hood and Quigley 2008). In the rat, selecting for low anxiety resulted in a highly aggressive line, which is hyperresponsive to social stress (Veenema et al. 2007b).

Each position or rank within a group is a result of natural forms of aggression and has a distinctive brain gene expression profile that correlates with behavioral phenotype (Sneddon et al. 2011). Furthermore, transitions in rank position shift gene expression within 48 h in concurrent with the new dominance status. In the bee brain, more than 2,000 genes related to aggressive behavior were found (Chandrasekaran et al. 2011). Transcription factors played key roles including well-known regulators of neural and behavioral plasticity, e.g., CREB, as well as factors known in other biological contexts, e.g., NF-κB (immunity).

Quantitative genetic models normally partition an individual's phenotype into genetic and environmental components (Wilson et al. 2009). However, in the case of social behavior, an individual's phenotype may well be determined (at least in part) by the genotypes of interacting conspecifics. In this way, by social interaction, the "environment" is itself filled with genes and may be expected to evolve under appropriate selection (Griffing 1976; Moore et al. 1997; Wolf et al. 1998). This perspective can be accommodated using "indirect genetic effect" models (Wilson et al. 2009), in which the trait of a focal individual is potentially influenced not only by its own genotype but also by that of other individuals with which it interacts (Moore et al. 1997). In this respect, repeatable differences in aggressive behavior were present among individuals of a mice population, and the phenotypic expression also depends on the genotype of the opponent individuals (Wilson et al. 2009).

The genetic background likely stabilizes the individual's socialization by giving a frame, in which environmental factors shape the personality and behavioral styles rather than predict behavior (Retz and Rosler 2009). Allelic variation is responsible for individual differences in neural functioning, resulting in a disposition for violent aggression or delinquent behavior. The genes' effects are not deterministic, but probabilistic and leave a wide margin for self-ruled decisions.

9.6.1 Studies in Knockout Animals

9.6.1.1 Sexual Steroids

The involvement of sexual steroids was supported by androgen receptor (AR) and ER knockout (KO) mice. Male mice exhibiting a spontaneous mutation that fails to produce the long form of the AR are not aggressive (Olsen 1983; Maxson 1999). Male mice with targeted disruption of the gene encoding the ERα display reduced

aggression in several testing situations due to the missing testosterone effect via estrogenic metabolites (Ogawa et al. 1997, 1998). Conversely, the ERβ-KO exhibits normal or increased aggression depending on social experience (Ogawa et al. 1999, 2000). ERα-KO females exhibit increased levels of aggression toward other female mice relative to wild-type females (Ogawa et al. 1997, 1998). Because estrogen is essential for the normal sexual differentiation of the CNS of male and possibly female mammals during development (Arnold 1996), studies of adult behavior in ER-KO are complicated by the inability to dissociate genetic from ontogenetic causes of behavior.

9.6.1.2 Serotonin

Male mice that lack functional expression of the 5-HT_{1B}-R attack an intruder more aggressively with a much shorter latency and higher frequency than the corresponding wild-type control (Saudou et al. 1994; Brunner and Hen 1997). Lactating female 5-HT_{1B}-R-KO mice also attack unfamiliar male mice more rapidly and violently (Ramboz et al. 1996). SER transporter knockout mice, where the reuptake of SER is diminished, wherefore its synaptic level is increased, show a reduction in aggressive behavior (Holmes et al. 2002).

Administration of a nonselective 5-HT_{1B}-R agonist (eltoprazine) significantly reduces aggressive behavior in both 5-HT_{1B}-R-KO and wild-type mice, suggesting the involvement of other receptor subtypes as well (Ramboz et al. 1996). Interestingly, mice lacking $5HT_{1A}$-Rs are less reactive, and possibly less aggressive, and show more anxiety-related behavior compared with wild-type mice (Zhuang et al. 1999), a finding consistent with the observation of increased postsynaptic 5-HT_{1A}-R availability in limbic and cortical regions of highly aggressive mice (Korte et al. 1996). These data do not elucidate, however, the known antiaggressive effect of 5-HT_{1A}-R agonists in rodents (Olivier et al. 1995; Miczek et al. 1998).

9.6.1.3 Molecules Connected to Serotonin

Lifelong disruption of several molecules results in changes in SER and other systems and in this way may affect aggression. It is probable that the role attributed to a genetic deficiency in aggressive behavior is actually a consequence of secondary effects in several systems. Thus, the following results should be handled accordingly.

Calcium/calmodulin-dependent kinase II (CaMKII) is a neural-specific signaling molecule found at pre- and postsynaptic regions. CaMK-mediated phosphorylation is involved in activation of tryptophan hydroxylase (TH), the rate-limiting enzyme in SER synthesis (Ehret et al. 1989). Accordingly, SER release is reduced in the dorsal raphe of α-CaMKII mutant mice (Cases et al. 1996). α-CaMKII knockout mice display reduced aggression in resident–intruder paradigms (Cases et al. 1996). Heterozygotes, in which only one copy of the α-CaMKII gene is missing, show normal offensive aggression and elevated defensive aggression (Cases et al. 1996).

MAO-A deficiency, caused by a point mutation in its coding gene, correlates with aggression in several males from a Dutch family (Brunner et al. 1993). Ablation of the gene encoding MAO-A in mice leads to high levels of offensive aggression (Mejia et al. 2002), in spite of elevated SER concentrations in juveniles and NA concentrations in adults (Cases et al. 1995). However, the metabolic disturbance caused by chronic MAO-A deficiency induces several alterations in these mutant mice (Cases et al. 1996; Holschneider et al. 2000), including upregulation of adenosine 2A receptors, and abnormalities of SER receptor subtypes (Bou-Flores and Hilaire 2000).

Both pharmacological and genetic evidences indicate a facilitatory role for central histamine via H1-receptors in aggression in connection with SER (Noguchi et al. 1992; Yanai et al. 1998). H1-receptor KO mice exhibit less aggression and increased SER turnover in several brain areas (Yanai et al. 1998).

Neural cell adhesion molecule (NCAM) is important during development and in adult neural plasticity (Goridis and Brunet 1992; Scholey et al. 1993). Both NCAM-KO and heterozygous NCAM mice display elevated anxiety and aggression (Stork et al. 1999; Stork et al. 2000). Lower doses of 5-HT_{1A}-R agonists are necessary to reduce anxiety and presumably aggressiveness in the NCAM-KO mice compared with wild-type mice, suggesting a functional change in the 5-HT_{1A}-R (Stork et al. 1999).

Transgenic male mice that overexpress the gene encoding human transforming growth factor-α (TGFα) exhibit enhanced aggressive behavior (Hilakivi-Clarke et al. 1992) accompanied by increased plasma estradiol concentrations and reduced SER turnover in the brain. Interestingly, the heightened aggressiveness in these mice is reversed with either SER uptake inhibitors (Hilakivi-Clarke and Goldberg 1993) or by castration (Hilakivi-Clarke 1994).

Nitric oxide (NO) also serves as an aggression-modulating neurotransmitter (Nelson et al. 1997). Male neuronal NOS-KO and wild-type mice in which nNOS is pharmacologically suppressed are highly aggressive (Nelson et al. 1995; Demas et al. 1997). Castration and testosterone replacement studies in both nNOS knockout and wild-type mice exclude an activational role for gonadal steroids in the elevated aggression (Nelson et al. 1995; Kriegsfeld et al. 1997). NO also appears to affect aggressive behavior via SER. Excessive aggressiveness and impulsiveness of nNOS-KO are caused by selective decrements in SER turnover and deficient 5-HT_{1A}-R and 5-HT_{1B}-R function in brain regions regulating emotion (Chiavegatto et al. 2001). It was possible that NO from endothelial tissue could also contribute to aggression; e.g., endothelial NOS-KO displays virtually no aggression even after pharmacological normalization of blood pressure (Demas et al. 1999).

9.6.1.4 Other Genes Involved in Aggression

The disruption of the V_{1b}, but not the V_{1a}, gene reduced intermale aggression, suggesting that the former, but not the latter, is involved in the control of aggression (Wersinger et al. 2007a, b).

In line with other studies on substance P and aggression, the NK1-KO mice are less aggressive (De Felipe et al. 1998). However, it could be the consequence to some secondary changes like an increase in SER function accompanied by a selective desensitization of 5-HT_{1A} inhibitory autoreceptors (Santarelli et al. 2001).

The most important cannabinoid receptor in the CNS is the CB1-R. CB1-R-KO mice presented an increase in the aggressive response measured in the resident–intruder test (Martin et al. 2002).

Interleukin-6 (IL-6) is a cytokine released by activated immune cells which has been shown to affect brain function (Alleva et al. 1998). IL-6-KO mice showed a higher degree of aggressive behavior, as indicated by a higher frequency of offensive upright posture. On the contrary, IL-6 overexpressing subjects showed a tendency to be more involved in affiliative-type social interactions. As secondary change, DA levels were found to be modified in a number of brain regions in IL-6-KO mice (Alleva et al. 1998).

9.6.2 Polymorphism

9.6.2.1 Sexual Steroids

The best established, highly polymorphic and functional locus with regard to sex determination is the AR, which embraces two trinucleotide repeats (Craig and Halton 2009). Both Jonsson et al. 2001 in healthy Swedish males and Rajender et al. 2008 in Indian males found an association of shorter (and presumptively higher expressed) CAG repeats with a somewhat more dramatic phenotype, verbal aggression, or violent criminal activity.

9.6.2.2 Serotonin System

One of the best-studied genomic variations in biological psychiatry is that of the polymorphism of the SER system. Genetic polymorphism of the TH gene, which is the rate-limiting enzyme of SER biosynthesis, is associated with individual differences in aggressive disposition in the normal human population (Manuck et al. 1999). Overall, individuals with an A-allele scored significantly higher on measures of aggression and tendency to experience unprovoked anger. The covariation of the TH1 genotype with aggression and anger measures was found to be statistically robust in men, but nonsignificant among women.

The synaptic activity of SER is terminated by the reuptake into presynaptic terminals, which occurs via the SER transporter (5-HTT) protein. The gene for 5-HTT in humans shows a relatively common polymorphism characterized by a variable repeat sequence in the promoter region, resulting in two common alleles: the short (S) variant comprising 14 copies of a 20–23 base-pair repeat unit and the long (L) variant comprising 16 copies (Lesch et al. 1996). The 5-HTT promoter sequence

polymorphism associates with differential transcription of the 5-HTT gene, with more efficient expression from the L-allele (Lesch et al. 1996; Greenberg et al. 1999). The 5-HTT-L variant has been shown to be associated with childhood aggression (Beitchman et al. 2006). Investigating the influence of both childhood psychosocial adversity and 5-HTT-L genotype, on the appearance of violent aggression in adult offenders, Reif et al. (2007) showed that homozygotes for the 5-HTT-L-allele were generally less likely to develop later-life violent behavior, while carriers of at least one S-allele were influenced by environmental factors.

The rhesus monkey shows a polymorphism in the 5-HTT promoter that is comparable in form and function to that in humans such that the S 5-HTT promoter variant in the monkey is also associated with decreased 5-HTT levels in brain (Lesch et al. 1997; Barr et al. 2003). Likewise, monkeys bearing the S version of the 5-HTT promoter polymorphism show reduced SER activity, increased impulsivity, and are more aggressive than animals bearing the L version of the promoter variant (Bennett et al. 2002; Champoux et al. 2002).

Regarding the SER receptors, there are a number of polymorphisms in the 5-HT_{1B}-R, and more than 20 association studies have been published with aggression with varying results (Sanders et al. 2002). There are several polymorphisms reported also for 5HT_{2A}-R; however, there is scant evidence for the functional importance of any (Craig and Halton 2009).

Polymorphism of a SER-degrading enzyme, MAO, was also discovered. Males maltreated during their youth were at higher risk of being convicted of a violent crime before 27 years of age if they had the short version of the functional polymorphism in the gene coding for MAO-A activity (Caspi et al. 2002). A study with adult males found the MAO-A–maltreatment interaction for antisocial behavior only for white subjects (Widom and Brzustowicz 2006). Another study found the same type of interaction for conduct disorder assessed during adolescence with a sample of male twins (Foley et al. 2004), and a third study with 7-year-old male twins found the significant gene–environment interaction for a composite mental health problem scale and attention deficit–hyperactivity disorder, but not for a total antisocial problem scale (Kim-Cohen et al. 2006). Thus, the MAO-A–maltreatment statistical interaction could depend on racial background and societal factors.

Several studies implicate a biallelic single nucleotide polymorphism of COMT, the other SER-degrading enzyme, with methionine (met) substituting for valine (val). This substitution increases violent behavior in a small subgroup of schizophrenic patients (Volavka et al. 2004). Recently, given the ambiguity of the data and the role of sex differences, Kulikova et al. 2008 examined the functional single nucleotid polymorphism in the manifestation of physical aggression in unselected women. They observed that the met/met homozygotes are least aggressive, while wild-type homozygotes (val/val) exhibited maximum aggression.

9.6.2.3 Other Candidates

Dopamine beta-hydroxylase (DBH) is a key enzyme in the synthesis of NA, and there is an abundance of literature describing the genetic control of DBH levels

(in serum) and some indication that this may underpin aspects of antisocial behavior. Hess et al. 2009 have provided evidence that a DBH polymorphism (1021TT) was significantly associated with increased neuroticism scores and impulsive or aggressive behavior.

In pigs, a single nucleotide polymorphism of the AVP V_{1b} receptor showed a highly significant association with aggressive behavior (Murani et al. 2010). Young and colleagues examined the sequence variations in the AVP V_{1a} receptor gene (Hammock and Young 2005; Donaldson and Young 2008). Among voles, subspecies differences in social behavior are associated with a sequence variation in the V_{1a} receptor gene and differential expression of the V_{1a} receptor. Reversing the pattern of V_{1a} receptor expression eliminates the differences in selected, AVP-mediated social behavior (Robinson et al. 2008). These studies describe a causal genotype–phenotype relation (Meaney 2010).

Among these variants, functional polymorphisms in the 5-HTT and MAO-A genes may be of particular importance due to the relationship between these polymorphic variants and anatomical changes in the limbic system of aggressive people. Furthermore, functional variants of 5-HTT and MAO-A are capable of mediating the influence of environmental factors on aggression-related traits. Indeed, the above mentioned results suggest that a 5-HTT polymorphism might have a role in balancing aggressive behavior in differing societies.

9.7 Environmental Effects, Epigenetic Mechanisms

The nature–nurture debate is an essential question of the determinants of individual differences in the expression of specific traits among members of the same species. The origin of the terms nature and nurture has been credited to Richard Mulcaster, a British teacher who imagined these influences as collaborative forces that shape child development (West and King 1987). For a long time, genetic and environmental influences were considered as independent agents in the field of development (Meaney 2010). Nowadays, it is widely accepted that these two factors are highly interconnected as environmental factors may induce heritable changes, although not inside the genetic code, but on the epigenome (Murgatroyd et al. 2010). Genetic studies attempt to understand the genome that is identical in different cell types and throughout life. Epigenetic studies, however, attempt to understand the epigenome that varies between cell type and during development and could explain change and stability as well (Tremblay and Hamet 2008). It is interesting that across species, increasing complexity is associated not so much with an increase in the number of genes that actively code for proteins, but rather with the size of the noncoding region of the genome. This difference may reflect the increased complexity of the regulatory regions of the DNA that, in turn, confers enhanced capacity for tissue-specific regulation of gene expression in multiorgan animals. In addition, the increased size of the regulatory region of the genome should also correspond to an increased capacity for environmental regulation of gene expression, a process whereby an increasing range of phenotypes might emerge from a common genotype: an increased capacity for phenotypic plasticity.

In fact, the activity–inactivity of the gene expression is highly influenced by environmental factors, and these changes through epigenetic modifications, e.g., DNA methylation or histone modification, may leave marks on the genome that are transmittable to the next generations. One of the key structures connecting environment with epigenome could be the HPA axis, namely, the glucocorticoids as end hormones (Auger et al. 2011). Epigenetic modifications might underlie a wide range of stable changes in neural function following exposure to highly salient events, e.g., chronic stress, drugs of abuse, reproductive phases such as parenting, etc., and are thus logical mechanisms for environmentally induced alterations in mental health (Tsankova et al. 2007; Jiang et al. 2008; Akbarian and Huang 2009). Although epigenetic regulation was first discovered in connection with development, fully mature neurons in an adult animal also express the necessary enzymatic machinery to demethylate or remethylate DNA (Meaney 2010). It is possible that environmentally driven changes in neuronal transcriptional signals could potentially remodel the methylation state of specific regions of the DNA (Meaney and Szyf 2005). Another important epigenetic mechanism, histone protein modification, is associated with exposure to drugs of abuse and stressors in rodent models (Renthal et al. 2007; Renthal and Nestler 2008).

It is worth to mention that epigenetic changes are important determinants of development not only during the beginning of life but also in aging (Murgatroyd et al. 2010). A relationship between DNA methylation and aging was originally proposed in a pioneering study by Berdyshev et al. (1967), which showed that genomic global DNA methylation decreases with age in spawning humpbacked salmon. In support of this finding, a gradual global loss of cytosine methylation has been detected in various mouse, rat, and human tissues (Vanyushin et al. 1973; Wilson et al. 1987; Fuke et al. 2004). Aside from global hypomethylation, a number of specific loci (in cytosine–guanine islands) have been reported to become hypermethylated during aging, e.g., the ribosomal gene cluster, the estrogen receptor, c-fos, etc. (Fraga et al. 2007). Study in humans has revealed that intraindividual changes in DNA methylation show some degree of familial clustering, indicative of a genetic component (Bjornsson et al. 2008). This suggests that at least some aspects of epigenetic changes are also genetically determined.

9.7.1 Epigenetic Mechanisms

Epigenetic modifications do not alter the sequence composition of the genome. Instead, epigenetic marks on the DNA and the other features of the chromatin regulate the operation of the genome. Thus, epigenetics has been defined as a functional modification to the DNA that does not involve an alteration of sequence (Meaney 2010). Most widely studied epigenetic controls are DNA methylation and histone acetylation, as, for example, lower methylation of a gene usually leads to increased mRNA expression (Rodenhiser and Mann 2006).

9.7.1.1 Histone Modifications

The histones and DNA together are referred to as chromatin, and the nucleosome is the organization of the chromatin (Meaney 2010). Under normal conditions, there is a tight physical relation between the histone proteins and its accompanying DNA, resulting in a rather closed nucleosome configuration. This restrictive configuration is maintained, in part, by electrostatic bonds between the positively charged histones and the negatively charged DNA. The closed configuration impedes transcription factor binding and is associated with a reduced level of gene expression. The activation of gene expression commonly requires chemical modification of the chromatin that occurs on the histone proteins. Chromatin remodeling is required for increased transcription factor binding to regulatory sites on the DNA and the activation of gene expression. The dynamic alteration of chromatin structure is achieved through modifications to the histone proteins at the tail regions that protrude outside of the nucleosome. This process is achieved through a series of enzymes that bind to the histone tails and modify the local chemical properties of specific amino acids along the tail (Grunstein 1997; Jenuwein and Allis 2001; Hake and Allis 2006). The enzyme histone acetyltransferase (HAT) transfers an acetyl group onto specific lysines on the histone tails. The addition of the acetyl group diminishes the positive charge, loosening the relation between the histones and DNA, opening the chromatin, and improving the ability of transcription factors to access DNA sites. Thus, histone acetylation at specific lysine sites is commonly associated with active gene transcription. The functional antagonists of the histone acetyltransferases are a class of enzymes known as histone deacetylases (HDACs). These enzymes remove acetyl groups and prevent further acetylation, thus serving to maintain a closed chromatin structure, decreasing transcription factor and gene expression. Although several other amino acid residues and mechanisms, like phosphorylation or ubiquitination, are involved, the best studied one is lysine acetylation.

9.7.1.2 DNA Methylation

The classic epigenetic alteration is that of DNA methylation, which involves the addition of a methyl group onto cytosines in cytosine–guanine (CpG) dinucleotides in the DNA (Razin and Riggs 1980; Bird 1986; Holliday 1989; Razin and Cedar 1993). The methylation of DNA is an active biochemical modification that in mammals selectively targets cytosines and is achieved through the action of a class of enzymes, DNA methyltransferases (DNMTs), which transfer the methyl groups from methyl donors. Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme in the generation of methyl groups for DNA methylation (Devlin et al. 2010). DNA methylation is a stable chemical modification, and it is associated with the silencing of gene transcription (Bestor 1998; Razin 1998; Bird and Wolffe 1999; Bird 2002). This effect appears to be mediated in one of two ways (Bird 2002). First, wide swaths of DNA can be methylated and the shear density of methylation precludes

transcription factor binding to DNA sites, thus silencing gene expression. The second manner is subtler, and probably far more prevalent, in regions with more dynamic variations in gene transcription, such as the brain. In this case, selected cytosines are methylated, and the presence of the methyl group attracts a class of proteins known as methylated-DNA binding proteins (Klose and Bird 2006). These proteins, in turn, attract an entire cluster of proteins, known as repressor complexes that are the active mediators of the gene silencing. The HDACs are a critical component of the repressor complex. HDACs prevent histone acetylation and favor a closed chromatin state that constrains transcription factor binding and gene expression. Compounds that inhibit HDACs can thus increase transcription from methylated DNA.

DNA methylation-induced gene silencing mediates two of the most commonly studied examples of epigenetic silencing, namely, X-chromosome inactivation and gene imprinting. During imprinting, the expression-specific genes are determined by the parent of origin via inactivation of one allele by methylation.

Although these processes seem to have a major impact on development, recently, it was established that DNA methylation patterns are actively modified in mature, i.e., fully differentiated cells, including and perhaps especially neurons, too, and that such modifications can occur in animals in response to cellular signals driven by environmental events (Meaney and Szyf 2005; Jirtle and Skinner 2007; Bird 2007). Both mature lymphocytes (Bruniquel and Schwartz 2003; Murayama et al. 2006) and neurons (Martinowich et al. 2003; Champagne et al. 2006, 2008; Lubin et al. 2008; Sweatt 2009) show changes in the DNA methylation patterns at critical genomic regions in response to environmental stimuli that stably alter cellular function. The ability of environmental signals to actively remodel epigenetic marks that regulate gene expression is a rather radical change in our understanding of the environmental regulation of gene expression. Such epigenetic modifications are thus a candidate mechanism for the environmental "programming" of gene expression. Although DNA methylation patterns may change during the perinatal period, methylation of some genes in the brain is considered a somewhat stable event that may require maintenance throughout the life span.

9.8 Epigenetic Changes in Aggression

Despite the recommendations made over 30 years ago (Fuller and Hahn 1976; Scott 1977), studies of the genetics of variation in aggressive behaviors have generally considered aggression as a characteristic of an individual, independent of the social context in which it is expressed (Hahn and Schanz 1996). However, the behavior expressed by an individual will usually depend on the behavior of the conspecific with which it interacts (see indirect genetic effect) (Wilson et al. 2009). On the other hand, the social learning theory of aggression says that children learn to aggress from their environment, i.e., the family, peers, neighborhoods, and the media (Bandura 1973; Reiss and Roth 1993; Anderson et al. 2003; NIH 2004; Tremblay 2008). The truth seems to be somewhere in between, in the epigenome.

9.8.1 Indirect Evidence on Epigenetic Mechanism in Aggression

The role of epigenetic mechanisms in the following processes could be assumed as there is a strong association between MTHFR, an enzyme required for folate metabolism, and the generation of methyl groups with global changes in DNA methylation (Frosst et al. 1995, 2002; Castro et al. 2004; Sohn et al. 2009; Devlin et al. 2010) and early intervention-induced impulsivity changes. Although most of the maternal-manipulation-induced epigenetic changes were associated with development of depression in offspring, we can assume a similar epigenetic association between early intervention and development of aggression, too.

Most of the epigenetic changes occur during early development, wherefore cross-fostering studies seem to be a good tool to dissect the effect of genetic and environmental/epigenetic changes. Manipulation of the mother–infant interaction is another widely used test to induce epigenetic changes in the offspring. Postweaning social isolation restricts environmental factors early in the development, thereby influencing gene expression most probably at epigenetic level. Indeed, postweaning social isolation induced a reduction of DNMT3b in mice.

9.8.1.1 Cross-Fostering

The nature vs. nurture question was examined in the middle of the twentieth century by cross-fostering mice with rats and studying the effects of the mother, preweaning peer group, and postweaning peer group (Denenberg et al. 1964, 1966; Hudgens et al. 1968). The results from these studies were very interesting in that they suggested that maternal interactions have a greater impact on the subsequent expression of behavior than did the genetic contribution (Hudgens et al. 1968). Indeed, mice reared by rats showed decreased aggression toward conspecifics (King and Gurney 1954; King 1957). The results suggested that the role of social context in the expression of social behavior is very important (Cushing and Kramer 2005). However, phylogenetic differences could confound the results.

Cross-fostering two mice strains, the more aggressive monogamous California mice to the less aggressive polygynous white-footed mice, the offspring showed decreased aggression as adults, and the decrease was correlated with a reduction in AVP immunoreactivity (Bester-Meredith and Marler 2001). Cross-fostering of white-footed mice to California mice resulted in the opposite pattern; aggression and AVP were increased.

9.8.1.2 Early Social Experience

"Stress diathesis" models are proposed as explanations for the relation between early experience and health (Seckl and Meaney 1993; Gorman et al. 2000; Heim and Nemeroff 2001; Meaney 2001, 2007; Repetti et al. 2002; McEwen 2003).

These models suggest that adversity in early life alters the development of neural and endocrine responses to stress in a manner that predisposes individuals to disease (Meaney 2010). Indeed, besides the widely studied depression in mood, disturbances of early mother–infant attachment relationships result in disturbance of social interaction including aggression (Veenema 2009).

The most severe early separation model consists of tactile social isolation during at least the first 6 months of life. These studies on monkeys were the first to demonstrate the devastating consequences of social isolation on normal development (Harlow et al. 1965). Isolated infants showed a total lack of exploration and social interaction, extreme high levels of fear, freezing in response to aggression of other animals, and self-directed and stereotypic motor activity (Mason and Sponholz 1963; Harlow et al. 1965, 1971; McKinney 1974; Seay and Gottfried 1975). As adolescents and adults, these monkeys exhibited excessive and inappropriate aggression toward other monkeys. Reversal of most of these early social isolation-induced behavioral deficits was observed when infants were exposed to a normal social environment within the first 6 months of life (Harlow and Suomi 1971; Cummins and Suomi 1976). In later studies, milder separation paradigms were also used. Hinde et al. (1966) demonstrated that a short separation of rhesus monkeys from their mothers continued to affect their interactions with their mothers weeks after being reunited. Female rhesus monkeys that are completely or partially deprived of maternal contact during the neonatal period, even if raised with peers, display significant changes in the expression of social behavior later in life (Seay et al. 1964; Suomi and Ripp 1983; Kraemer 1992; Kraemer and Clarke 1996). They are more aggressive, more likely to withdraw from novel social interactions and to abuse or neglect their own offspring than monkeys raised by their mothers. Nursery-reared rhesus monkeys show an increase in agonistic behaviors and stereotypy and a reduction in reciprocal social interactions relative to mother-reared monkeys (Winslow et al. 2003).

In male Wistar rats, exposure to maternal separation (3 h/day, days 1–14) induced an increase in aggressive behaviors at juvenile (play fighting) and adult (intermale aggression) age (Veenema et al. 2006; Veenema 2009). Play fighting is an essential behavior for the development of adequate adult social behaviors (Meaney and Stewart 1979; Panksepp et al. 1984; Vanderschuren et al. 1997) and consists of behavioral patterns related to adult aggressive behaviors (Panksepp et al. 1984; Pellis and Pellis 1987; Vanderschuren et al. 1997). At juvenile age, maternal separation increased the number of attacks toward the nape of the neck, decreased the number of supine behaviors, a submissive play behavior, and induced the emergence of offensive pulling and biting, a behavior hardly expressed by controls, toward an unknown age-matched play partner during the resident–intruder test (Veenema 2009). In adulthood, maternally separated rats showed significant increases in key elements of aggression, including lateral threat, offensive upright, and keep down, when being exposed as a resident to an unknown male intruder rat (Veenema et al. 2006). These data indicate that maternal separation promotes the expression of aggressive behaviors in male rats across development.

In contrast to male rats, maternal separation of C57Bl/6 mice induced a decrease in intermale aggression, as shown by longer attack latencies in maternally separated

adult males compared with control males (Veenema et al. 2007a). However, maternal separation of C57Bl/6 mice induced an increase in maternal aggression towards a male CD1 intruder mouse during the first week of lactation (Veenema et al. 2007a).

9.8.1.3 Postweaning Social Isolation

In most laboratories, postweaning social isolation is performed by housing rat or mouse pups in individual cages from the first day of weaning from the dam (between postnatal days 21 and 28) for a period of 4–8 weeks. Isolated rats or mice are normally reared in a room with other isolated-reared or group-housed rats or mice. Thus, isolation-reared rats or mice have visual, auditory, and olfactory contact with other conspecifics, but they are restricted from any form of physical interaction with their conspecifics. Postweaning social isolation was shown to induce changes in a wide variety of nonsocial behaviors, including hyperreactivity to a novel environment, impaired prepulse inhibition of acoustic startle, increased ethanol intake, and increased anxiety (Lapiz et al. 2001; Fone and Porkess 2008). Moreover, postweaning social isolation altered several social behaviors. For example, postweaning socially isolated males showed reduced levels of play fighting and social grooming (Von Frijtag et al. 2002), reduced submissive behaviors toward residents (van den Berg et al. 1999), and increased aggressive behaviors toward conspecifics in dyadic interactions or when being placed in a colony (Luciano and Lore 1975; Day et al. 1982; Wongwitdecha and Marsden 1996; Vale and Montgomery 1997; Bibancos et al. 2007).

9.8.2 Epigenetic Modifications in Molecular Mechanisms Connected with Aggression

9.8.2.1 Sexual Steroids

The early testosterone treatment of the eggs increased the frequency of aggression, dominance, and sexual behavior of 1-year-old, reproductively competent house sparrows. These hormone-mediated maternal effects were supposed to be an epigenetic mechanism causing intrasexual variation in adult behavioral phenotype (Partecke and Schwabl 2008). Indeed, epigenetic modifications have been implicated in sexual differentiation of the brain (McCarthy et al. 2009; Murray et al. 2011). Many neural sex differences depend on testosterone exposure during early postnatal life (Cooke et al. 1998), and steroid hormones are assumed to work, at least in part, by orchestrating changes in the epigenome (Spencer et al. 1997; Kishimoto et al. 2006). Sexual differentiation of the BNST in mice appears to require histone acetylation, as inhibiting histone acetylation blocks the masculinization of the BNST (Murray et al. 2009; Auger et al. 2011).

Another important contributor of the masculine phenotype is the ERα receptor. The ERα gene promoter contains multiple CpG sites that are potential targets for

DNA methylation. Sexually dimorphic ERα promoter methylation and deacetylation of histones regulating the expression of the ERα appear to be partly responsible for the sexually dimorphic expression of this receptor (Pinzone et al. 2004; Kurian et al. 2010; Westberry et al. 2010). Champagne et al. (2006) found increased cytosine methylation across the ERα-gene promoter in the offspring of low-maternal care mothers in MPOA.

Castration of adult male rats, known to reduce aggression by removal of testosterone, resulted in decreased AVP mRNA expression and increased methylation within the AVP promoter in the BNST (Auger et al. 2011). Similarly, castration significantly increased ERα mRNA expression and decreased ERα promoter methylation within the BNST. These changes were prevented by testosterone replacement. This suggests that the DNA promoter methylation status of some steroid-responsive genes in the adult brain is actively maintained by the presence of circulating steroid hormones. The maintenance of methylated or demethylated states of some genes in the adult brain by the presence of steroid hormones may play a role in the homeostatic regulation of behaviorally relevant systems.

9.8.2.2 Serotonin

The 5-HTT-L variant has been shown to influence vulnerability to the impact of early stressful life events (see earlier). The methylation status of its promoter was shown to play a role in governing 5-HTT mRNA levels (Philibert et al. 2007; Devlin et al. 2010). Depressed mood during the second trimester of human pregnancy was associated with reduced methylation of the maternal and neonatal 5-HTT gene promoter region measured in the whole blood. Conceivably, such reduced methylation may lead to increased 5-HTT expression and availability of 5-HTT and as such result in increased SER reuptake and lower intrasynaptic SER. In the mature brain, this might not have a noticeable impact, but in the developing brain, such altered serotonergic tone may have long-term effects on behavior, as prior to the neurotransmitter role of SER, it plays critical roles as a trophic factor modulating neuronal differentiation and growth (Ansorge et al. 2008).

9.8.2.3 Vasopressin and the Stress Axis

Early life stress in mice (daily 3-h separation of mouse pups from their mother during postnatal days 1–10) caused persistent epigenetic marking (hypomethylation) of a key regulatory region of the AVP gene in the PVN underpinning sustained upregulation of AVP mRNA expression and increased HPA axis activity (Murgatroyd et al. 2009; Murgatroyd and Spengler 2011). Hypomethylation of the AVP promoter is achieved through phosphorylation of methyl CpG-binding protein 2 (MeCP2) (Cloud 2010). The early-life stress-induced endocrine phenotype lasted for at least 1 year following the initial adverse event. Although treatment with an AVP V_{1b} receptor antagonist reversed the mice's phenotype, but the epigenetic marking of the methylation landmarks in the AVP enhancer persisted, suggesting that early-life stress has engraved a

permanent memory trace that conferred lifelong susceptibility to stress (Murgatroyd et al. 2009). Although it is clear that the epigenetic control of AVP cells in the PVN is sensitive to stress hormones during early development, it is unclear whether stress hormones alter DNA methylation patterns in adulthood within these cells.

Lower sensory input from the mother was accompanied by enhanced methylation of the CRH promoter in the hippocampus of the offspring (McClelland et al. 2011). Notably, enhanced methylation is generally associated with reduced transcription, whereas CRH gene expression was enhanced in this group that performed worse in learning and memory tests later in life.

Maternal undernutrition, as an early-life stress, may also induce epigenetic changes (Stevens et al. 2011). Not only histone acetylation but also hypomethylation of the POMC gene was detected. Parallel hypomethylation of the hypothalamic glucocorticoid receptor (GR) suggests that it might mediate regulation of a number of hypothalamic neuropeptides including POMC and neuropeptide Y.

Disturbances of early social development may alter the methylation at the GR gene promoter in the hippocampus (Weaver et al. 2004). SER, as a classic neurotransmitter responding dynamically to environmental signals, was found to regulate GR expression via epigenetic mechanisms (HAT) (Meaney 2010).This effect can be reversed by central infusion of a HDAC inhibitor, thereby normalizing the stress responses.

9.8.2.4 Neurotrophins

Neurotrophins, such as NGF and BDNF, which play a fundamental role in brain function and neuroprotection and are affected by stress, are good candidates for transducing the effects of adverse events in changes of brain function (Cirulli et al. 2009). Early adversive events may induce changes in NGF levels, which is accompanied by HPA axis dysregulation, a process, which is probably mediated by epigenetic mechanisms (Aloe et al. 1994a; Branchi et al. 2004). Indeed, the NGF pathway is able to induce histone modifications (methylation and acetylation) in cell lines, resulting in changes in opioid receptor expression (Chen et al. 2008; Park et al. 2008). During differentiation induced by in vitro NGF treatment, the mRNA and protein levels of de novo methyltransferase DNMT3b increased, whereas those of DNMT3a and DNMT1 decreased (Bai et al. 2005). Human studies also confirmed the role of NGF in diverse psychological stress, like acute alcohol, heroin, or nicotine withdrawal (Aloe et al. 1996; Lang et al. 2002). The CpG island promoter methylation of the NGF gene significantly increased in the blood of alcohol-dependent patients together with an increase in NGF serum levels (Heberlein et al. 2011).

Expression of BDNF in a rat model was shown to be sensitive to early adverse life experience, an event regulated by methylation (Roth et al. 2009). Although several epigenetic modifications of the BDNF promoter were confirmed, most of the studies were focusing on the hippocampus and depressive-like symptoms (Boulle et al. 2011). However, based upon the aforementioned role of BDNF in aggression, we might assume an epigenetic regulation of the BDNF promoter in the development of the aggressive phenotype, too.

9.8.2.5 Other Putative Mechanisms

In one study, boys from low socioeconomic background, who were found to be on a high physical aggression trajectory, were compared with boys from the same background, who followed a normal physical aggression trajectory (Broidy et al. 2003). Males on the chronic physical aggression trajectory have substantially more methylated alleles measured on T cells, more specifically on the interleukin-1B (IL-1B) cytokine gene.

The most serious self-aggression is suicide, where a significant reduction of the hippocampal GR was showed, which enhances HPA activity. This exaggerated stress response is—in the long run—the result of an increased DNA methylation of the promoter of the GR (Turner and Muller 2005).

9.8.3 Valproate Treatment

The epigenetic machinery seems to be a good target for therapeutical interventions; however, presently only few drugs are available with unspecific targets. Most of the research focused on VPA, an anticonvulsant, used in the treatment of epilepsy and bipolar disorder which, besides an effect on GABA neurotransmission, is an inhibitor of HDAC. HDAC inhibition leads to a global increase in the level of histone acetylation, which is most consistently associated with increased gene expression.

VPA administration reduces aggressive behavior in mice and rats (Sulcova et al. 1981; Oehler et al. 1985; Molina et al. 1986; Belozertseva and Andreev 1997). One of the possible background changes could be the enhanced AVP tone after VPA treatment (Murray et al. 2011).

Vehicle-treated male mice socially isolated for 2–3 weeks were very aggressive toward an untreated intruder of the same sex. Administration of met, a methyl donor enhancing the overall level of DNA methylation, to resident mice during the isolation period significantly prolonged the latency of attacks (Tremolizzo et al. 2005). This reduction of aggression was prevented by VPA coadministered with met. A VPA–met-treated resident attacked the intruder with a similar latency and duration as a vehicle-treated resident, whereas VPA alone in this experiment failed to modify aggressive behavior. The met-induced modification of aggressive behavior was dose related and persisted longer than 1 week following met withdrawal.

9.9 Conclusions

Aggression is an adaptive response to social challenges of the environment. However, pathological forms, mostly associated with other psychological disturbances, are highly destructive. Several brain regions (like HAA, MeA, PAG) and several molecules (testosterone, SER, AVP, etc.) are involved in the development of this behavior,

but one of the most important determinants is the behavior of the encounter. Therefore, it is not surprising that epigenetic changes, connecting environment with gene activation, could be highly involved in fine-tuning the brain structures and molecular network taking part in aggression. Till now, most of the knowledge accumulated on the involvement of different genes and the participation of epigenetic mechanisms in the development of aggressive behavior could be only supposed based on indirect data.

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