Where in the serotonergic system does it go wrong? Unravelling the route by which the serotonergic system affects feather pecking in chickens

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A B S T R A C T

A deficient serotonergic system is associated with psychopathological behaviors in various species, among which, feather pecking (FP) in chickens. Deficiency in the serotonergic system can predispose birds to develop FP, while the serotonergic system is affected in birds that feather peck. Serotonin (5-HT) can further influence dopamine (DA) activity. Lines with high FP tendency generally have low central 5-HT and DA turnovers at a young age, but high turnovers at an adult age in brain areas involved in somato-motor regulation and goal-directed behavior. Agonizing 5-HT1A and 5-HT1B receptors increases FP, while antagonizing D2 receptor reduces FP. Genetic associations exist between FP, 5-HT1A and 5-HT1B receptor functioning and metabolism of 5-HT and DA. Birds with deficient functioning of the somatodendritic 5-HT1A autoreceptor and 5-HT metabolism appear predisposed to develop FP. Birds which feather peck often eat feathers, have low whole-blood 5-HT, different gut-microbiota composition and immune competence compared to non-peckers. FP and feather eating likely affect the interaction between gut microbiota, immune system and serotonergic system, but this needs further investigation.

1. Introduction

The serotonergic system contains the central neurotransmitter and peripheral signaling molecule serotonin (5-hydroxytryptamine: 5-HT). Central 5-HT is a neurotransmitter with diffuse afferent projections from the raphe nuclei (RN) to various brain areas, thereby having a role in many processes such as appetite, food intake, mood, reproduction, pain, sleep and growth (Angoa-Perez et al., 2012; Berger et al., 2009; Dalley and Roiser, 2012; de Boer, 2009; Gillette, 2006). Central 5-HT regulates in part, also dopamine activity (3,4-dihydroxyphenethylamine: DA) in several brain areas (De Deurwaerdère and Di Giovanni, 2017; Matsunami et al., 2012; Navailles and De Deurwaerdère, 2011; Yadid et al., 1994). Central 5-HT hereby indirectly affects the motivation for reward related behaviors, a major function of DA (Kalenscher et al., 2005). Peripheral 5-HT can be found in several organs, thereby playing part in various physiological functions such as energy metabolism, pain perception, and bone remodeling (for review see Spohn and Mewe, 2017). The majority of 5-HT can be found peripherally in blood platelets and in enterochromaffin (EC) cells of the gastrointestinal tract (i.e. 95% of peripheral 5-HT is stored in EC cells (Mohammad-Zadeh et al., 2008)). Here, gut 5-HT is released from EC cells upon mucosal stimulation, and acts as an important signaling molecule influencing gut motility, vasoconstriction/dilatation, secretion, inflammation and immune regulation (Bornstein, 2012; Coates et al., 2017; Shajib and Khan, 2015). Central and peripheral 5-HT act independently, but can also interact via the bloodstream (as affected by

Abbreviations: 3-MT, 3-methoxytyramine; 5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin (5-hydroxytryptamine); 5-HTP, 5-hydroxy-L-tryptophan; Am, amygda; Ap, arcopallium; Arch, archistriatum; ATD, acute tryptophan depletion; BBB, blood-brain-barrier; Cl, control line of the LML; CNS, central nervous system; CORt, corticosterone; DA, dopamine (3,4-dihydroxyphenethylamine); DOPAC, 3,4-dihydroxyphenylacetic acid; Dr, dorsal thalamus; DW, Dekalb White; DXL, Dekalb XL; EC, enterochromaffin; FP, feather pecking; GM, gut microbiota; HFP, high feather pecking; HGPS, high group productivity and survivability; HP, high pecking; Hpc, hippocampus; HVA, homovanillic acid; Hy, hypothalamus; IL, interleukin; L-DOPA, L-3,4-di-hydroxyphenylalanine; LFP, low feather pecking; LGPS, low group productivity and survivability; LML, low mortality line; LNAA, large neutral amino acid; LP, low pecking; MAO, monoamine oxidase; mSt, medial striatum; NAc, nucleus accumbens; NCC, cauda-central nidopallium; NCL, caudo-lateral nidopallium; NE, norepinephrine; OCD, obsessive compulsive disorder; PHE, phe-nylalanine; RIR, Rhode Island Red; RN, raphe nuclei; SCFA, short-chain fatty acids; SERT, serotonin transporter; SNP, single nucleotide polymorphism; SSRI, selective serotonin reuptake inhibitor; TH, tyrosine hydroxylase; TI, tonic immobility; TPH, tryptophan hydroxylase; TRP, tryptophan; TTM, trichotillomania; TYR, tyrosine; WL, White Leghorn

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hormones, cytokines, enzymes, short-chain fatty acids (SCFA)), gut microbiota and vagus nerve activation (Coates et al., 2017) (see Fig. 1). They further share similar characteristics in their transporter, receptors, metabolite and are synthesized from their precursor tryptophan (TRP) (Berger et al., 2009). TRP is an essential amino acid, indicating that synthesis of both central and peripheral 5-HT is limited by the level of TRP in the diet (Young and Leyton, 2002).

Serotonin is essential to many homeostatic physiological processes while alterations, mainly in central 5-HT functioning, affect many pathological behaviors, directly or indirectly via its effects on DA. A vast amount of scientific evidence shows that dysfunctioning of central 5-HT and DA activity is key to a variety of mental disorders (Yildirim and Derksen, 2013). Deficient activity of central 5-HT is presumed causal in excessive aggression, impulsive and compulsive behavior (Fineberg et al., 2010; Potenza et al., 2009). Compulsive behavior is difficult to disrupt and often occurs under stress in predisposed subjects (Boulougouris et al., 2009). TRP is an essential amino acid, indicating that synthesis of both central and peripheral 5-HT is limited by the level of TRP in the diet (Young and Leyton, 2002).

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injuries in victims and in extreme cases to cannibalistic pecking (Savory, 1995). In this review, we refer to severe FP as FP. Cannibalistic pecking occurs also independently from FP and can occur during vent pecking. Vent pecking is the act of pecking at the vent of other birds, during the process of egg laying. Vent pecking causes tissue damage to the cloaca mucosa and can develop into cannibalistic pecking. Aggressive pecking is distinct from FP by having a different underlying motivation (i.e. establishing hierarchy) and is directed to the head and comb area rather than to the bird’s back area as often occurs during FP (Rodenburg et al., 2013). Different forms of pecking can co-occur, but cannibalistic pecking, aggressive pecking, gentle and severe FP are presumed to have different underlying motivations (Buitenhuis and Kjaer, 2008; Savory et al., 1999).

2.1. Feather pecking: a redirected foraging behavior

Feather pecking is considered a redirected foraging behavior (Rodenburg et al., 2013). Foraging is the act of searching for food, shown in chickens by active walking, pecking, scratching and ingesting edible items i.e. food intake. Food intake is regulated by central 5-HT and DA, with central 5-HT being involved in satiety and meal termination, and DA in meal initiation (Meguid et al., 2000). Central 5-HT and DA interact in controlling feeding behavior (Zendehdel et al., 2017). Increasing central 5-HT, its metabolite 5-hydroxyindoleacetic acid (5-HIAA) and 5-HT turnover (5-HIAA/5-HT) in the diencephalon of chicks by intracerebroventricular injection of TRP or 5-HT has been shown to inhibit food intake (Bungo et al., 2008; Zendehdel et al., 2017). Co-injection of 5-HT and Prazosin (an adrenergic receptor antagonist) weakens the 5-HT effect on food intake in chicks (Zendehdel et al., 2017, 2016). As 5-HT and DA are both involved in appetite and food intake in chicks, it is highly likely that these systems play part in foraging behavior in this species. Indeed, injection of S-15535 (somatodendritic 5-HT1A autoreceptor agonist and postsynaptic 5-HT1A receptor antagonist) decreased 5-HT turnover in the hippocampus (Hpc), archistriatum (Arch) and remainder of forebrain, and increased foraging and FP in chicks (van Hieren et al., 2004a). Foraging is considered a highly motivated behavior for chicks (Cooper and Albentosa, 2003; de Jong et al., 2007). DA likely stimulates food searching and feeding motivation via its influence on appetite and facilitating rewarding behavior (Ikeymo and Panksepp, 1996; Palmer, 2007). Birds selected on high feather pecking (HFP) show not only more FP (Kjaer and Sorensen, 2002), but also more explorative pecking (de Haas et al., 2010) and they peck more in an operant conditioning test to obtain mealworms compared to birds selected on low feather pecking (LFP) (Hausler and Harlander-Matauschek, 2008). HFP birds are also highly active in various behavioral tests (Kops et al., 2017; van der Eijk et al., 2018) and in their home pen (Kjaer, 2009). These specific lines have been suggested as a hyperactivity disorder model (Kjaer, 2009), as supposedly mainly affected by DA dysfunctioning (Kjaer et al., 2015). The aforementioned studies give support to the assumption that FP is a form of redirected feeding/foraging behavior that is controlled by central 5-HT and DA.

2.2. Feather pecking: a maladaptive behavior

Maladaptive behavior is a behavior that occurs in order to cope with a thwarted environment (Mills, 2003). When the environment lacks the ability for hens to forage (for example lack of floor substrate), this can lead to FP (reviewed by Nicol et al., 2013). When in a thwarted environment, a hen’s foraging motivation cannot be fulfilled, foraging pecks can be redirected to the plumage of her group-mate(s). As such, fixed motor patterns of foraging and FP appear similar (Dixon et al., 2008). Feather pecking under suboptimal foraging conditions thus reflects a maladaptive behavior.

An animal’s ability to cope with a thwarted environment depends on how it deals with various stressors (i.e. coping style: Koolhaas et al., 2007). The way in which animals cope with stressors (i.e. reactive or proactive) may influence FP. Behavior of hens of high FP lines have been suggested to reflect a proactive coping style (de Haas et al., 2010; Kops et al., 2017; Korte et al., 1997; van der Eijk et al., 2018), although behavior of individual birds which show FP does not necessarily reflect proactive coping (Forkman et al., 2004). A proactive coping style has been linked to 5-HT and DA dysfunctioning (Coppens et al., 2010). Specifically, a proactive coping style relates to deficient 5-HT1A receptor functioning (Koolhaas et al., 2007; Puglisi-Allegra and Andolina, 2015; Vindas et al., 2017) and DA signaling (Giorgi et al., 2003; Höglund et al., 2017). Animals with a proactive coping style are more inclined to be aggressive, impulsive and to develop stereotypes under chronic stress (Geverink et al., 2003; Korte et al., 2005), whereas animals with a reactive coping style are more inclined to develop depression and anhedonia under chronic stress (de Boer et al., 2017; Koolhaas et al., 2007; Korte et al., 2005). The behaviors executed by animals with different coping styles may be equally effective in dealing with a stressor, but their success in coping varies per environment (Mendl et al., 2010). In humans, TTM under stressful conditions is seen as a way of proactive coping (Alexander et al., 2017). In summary, FP can be seen as a maladaptive behavior, i.e. as an attempt to cope with a thwarted environment, which has been linked to deficiencies in 5-HT functioning.

2.2.1. Interaction stress, central serotonin and maladaptive feather pecking

Stress can affect central 5-HT activity (Korte et al., 2005). In rodents, elevation of glucocorticoid hormones (i.e. corticosterone: CORT) as a consequence of stress can decrease tryptophan hydroxylase activity (TPH; enzyme that converts TRP to 5-hydroxy-L-tryptophan (5-HTP)) and central 5-HT tone (Chen et al., 2017). Furthermore, CORT can affect serotonergic activity by increasing sensitivity of 5-HT1A receptors (Meijer and de Kloet, 1998) and by decreasing SLC6A4 expression (gene coding for SERT) (Borue et al., 2007). Stress factors, such as social stress, can further influence peripheral 5-HT in chickens. For example, within group-aggression causes stress – shown by increased CORT – in hens (de Haas et al., 2012) and influences hens’ peripheral TRP and TRP/(PHE + TYR) ratio (PHE: phenylalanine and TYR: tyrosine)(Birkl et al., 2017a), thereby potentially affecting 5-HT synthesis. In response to social stress, low group productivity and survivability (LGPS) birds had higher plasma DA and CORT compared to high group productivity and survivability (HGPS) birds (Cheng et al., 2002). These lines also differ in central 5-HT and DA functioning (Dennis et al., 2008; Dennis and Cheng, 2012). Further, Lutz et al. (2016) showed that genetic correlations between FP, locomotion and feather eating is strongly affected by environmental effects. Being successful in coping with (social) stress may thus limit the risk of developing FP as a maladaptive behavior in hens.

2.3. Feather pecking: a malfunctioning behavior

A malfunctioning behavior is a pathological behavior that occurs relatively irrespective of the animal’s environment, and is strongly related to an individual’s predisposition. An individual’s predisposition to develop FP as a malfunctioning behavior could be caused by the individual’s (epi) genetic set-up. Feather pecking is moderately heritable (Kjaer and Sorensen, 2002) and epigenetic modulation is likely involved (Rodenburg and de Haas, 2016). Epigenetic alterations can influence various behavior patterns in chickens (Jensen, 2014) and malfunctioning stereotypic behavior in birds (Bateson et al., 2004). Stress in the maternal hen can lead to epigenetic modifications which affects behavior and stress responses in the offspring (Henriksen et al., 2011). In young chickens, exposure to elevated CORT during incubation resulted in lower whole-blood 5-HT and higher platelet 5-HT uptake as compared to saline treated chickens (Ahmed et al., 2014). On a flock level, maternal birds with high whole-blood 5-HT and high plasma CORT were found to have offspring which are more anxious and
perform more FP already at one week of age compared to offspring from maternal birds with low whole-blood 5-HT and low plasma CORT levels (de Haas et al., 2014b). On an individual level, it is known that stress in parental birds can affect gene methylation, gene expression and behavior of the offspring and grand-offspring in chicken and quail (Goerlich et al., 2012; Guibert et al., 2012; Lindqvist et al., 2007; Nätt et al., 2009). Preliminary results show differences in methylated genes in the hypothalamus (Hyp) between HFP and LFP birds (De Haas et al. unpublished results), which suggest epigenetic effects on FP. However, more evidence is needed to unravel whether and how epigenetic modulation, via egg hormones, and other forms of epigenetic modifications play a role in FP (Rodenburg and de Haas, 2016).

Alterations in functioning of 5-HT system may lead to FP or associated malfunctions, such as excessive aggression and anxiety. For example, in-ovo injection of 5-HT during incubation reduces chick aggression and increases tissue level of 5-HIAA, DA and DA turnover in the Hyp (Dennis et al., 2013a). Excessive aggression in rodents is a form of malfunctioning behavior related to deficient 5-HT system and a proactive coping style (Koolhaas et al., 1999). Although FP and aggression in chickens appear different in origin, some studies have also found consistent evidence for alterations in 5-HT1A and 5-HT1B receptor functioning in aggression and FP, but only in a highly aggressive line (Dennis and Cheng, 2012). FP may be similarly affected by alterations in the serotonergic system, as shown in extremely aggressive rodents and chickens. Thereby FP reflects a pathology influenced by a dysregulated 5-HT system, similar to aggression.

Genetic and phenotypic associations have also been found between high anxiety at a young age and FP at an adult age (Rodenburg et al., 2004a). Anxiety is a sustained high tendency to be fearful (Clement and Chapoutier, 1996; Korte, 2001; Korte et al., 2009; Reiss et al., 1986). Birds of a line which are more likely to peck conspecifics and perform cannibalism are more anxious at a young age than birds less likely to peck conspecifics (de Haas et al., 2012; Rodenburg et al., 2009b). Low central 5-HT activity appears predisposing for anxiety (Lucik, 1998). In humans, alterations in TPH, SERT, monoamine oxidase (MAO; enzyme that metabolizes 5-HT to 5-HIAA) and somatodendritic 5-HT1A auto-receptor functioning have been related to anxiety (Borne et al., 2007).

Broiler chickens selected on long tonic immobility (TI; death feigning fear response) show lower hypothalamic expression of the gene SLA6C (encoding SERT) and the HTR1A gene (encoding the somatodendritic 5-HT1A autoreceptor) than chickens selected on short TI (Wang et al., 2014). Furthermore, layers exhibit longer TI when exposed to 5-MT (5-methoxytriptamine; a 5-HT1, 2, 4, 6, 7 receptor agonist) (Dennis et al., 2013b), and high fear roosters have lower levels of plasma 5-HT than low fear roosters (Agnvall et al., 2015). Animals with high anxiety can develop a psychopathology such as FP (Korte et al., 2009; Pryce and Feldon, 2003) irrespective of their environment.

In summary, the tendency to develop FP appears pre-set by a chicken’s (epi) genetic background which can further create a (epi) genotype*environment sensitivity. Certain lines of commercial hybrids seem more sensitive to develop FP as a maladaptive behavior, while others are more sensitive to develop FP as a malfunctioning behavior (see Fig. 2). For example, ISA Brown hens are strongly influenced by social factors (group composition, (Uitdehaag et al., 2011, 2009); group size, (de Haas et al., 2013), and litter disruption (de Haas et al., 2014a)). These environmental challenges create a risk for the development of FP as a maladaptive behavior. Dekalb White (DW) hens have a high (epi)genetic predisposition for development of FP as a malfunctioning behavior, relating to anxiety and low whole-blood 5-HT, central 5-HT and DA compared to ISA Brown (de Haas et al., 2014b, 2013; Uitdehaag et al., 2011). Feather pecking can thus derive as a form of maladaptive behavior due to a thwarted or stressful environment as well as a form of malfunctioning behavior due to (epi) genetic predisposition.

3. Genetic evidence for involvement of the serotonergic system in feather pecking

Birds differing in pecking tendency have shown to differ in gene expression and in genetic background considering genes important for functionality of the serotonergic system.

3.1. Gene-expression related to the serotonergic system in birds with diverging pecking tendency

The most recent study on FP identified eight genes differently expressed in the whole brain of HFP and LFP birds (Lutz et al., 2017). Potential candidate genes were SLC12A9 (encode electroneutral cation – chloride cotransporters) and GNG2 (encoding G protein subunit gamma 2 gene) related to high aggression and FP, respectively. Family of SLC12 genes control transporters which cause a reduction of postsynaptic GABA-A receptor current (Medina et al., 2014). This effect is similarly caused by 5-HT via 5-HT2C receptors (Feng et al., 2001). The GNG2 gene encodes gamma subunits of a guanine nucleotide-binding protein, which are important for signaling across membranes. According to Lutz et al. (2017), the GNG2 gene is involved in postsynaptic signaling at 5-HT synapses, and emphasized as candidate gene for FP. Wysocki et al. (2013) found that the HTR1B gene was upregulated and the MAO-A gene was downregulated in the whole brain of HFP birds compared to LFP birds. The HTR1B gene encodes the G-protein coupled 5-HT1B receptor. HTR1B manages release of 5-HT (Olivier and Van Oorschot, 2005). The MAO-A gene encodes MAO-A enzymes catalyzing deamination of amines as 5-HT, DA and norepinephrine (NE). Hughes and Buitenhuis (2010) also compared gene-expression in the whole brain of HFP and LFP birds, but did not find differences in expression in genes related to 5-HT or DA system. They found that the PDZD2 gene (encoding endoplasmatic protein) was positively correlated to severe FP in the HFP line. Although not specific to the serotonergic system, PDZD2 gene is similar in sequence and protein encoding as the pro-interleukin-16 gene. Interleukins (IL) are cytokines, which are key signaling molecules of the immune system. In feather peckers genes involved in the immune system (LAG3 (encoding immune regulatory receptors); MAPK8 and TNFSF15 (tumor necrosis factor regulating genes) were upregulated in the Hyp compared to victims (Brunberg et al., 2011). These genes are involved in intestinal inflammation (Yuan et al., 2017). Intestinal inflammation is said to be regulated by gut 5-HT (Bornstein, 2012; Coates et al., 2017; Shajib and Khan, 2015). Although no direct link between FP and genes encoding central 5-HT was found in this study, they also showed that feather peckers had higher expression of genes associated with glucose metabolism and obsessive-compulsive disorder (OCD) compared to victims and neutrals (Brunberg et al., 2011). OCD is related to deficiency in 5-HT functioning in mammals (Boulogouros et al., 2009; Joel, 2006). Hereby, upregulation of OCD related genes in feather peckers indirectly links to deficiency in 5-HT functioning.

3.2. Genetics related to the serotonergic system in birds with diverging pecking tendency

Birds which differ in pecking tendency also have a different genetic makeup. For example, see the animal genome database for QTls identified for FP at https://www.animalgenome.org. When comparing the HFP and LFP line, two sub-haplotypes were found for the DRD4 gene (encoding the dopamine D4 receptor) and DEAF-1 (encoding deformed epidermal autoregulatory factor 1 homolog) (Flisikowski et al., 2009). These sub-haplotypes were linked to FP. The DEAF-1 protein represses the gene encoding the somatodendritic 5-HT1A autoreceptor promoter (Albert et al., 2011). Feather damage (as a proxy for FP, Bilcik and Keeling, 1999) has been associated with thirteen clusters of single nucleotide polymorphisms (SNPs) in a F2 cross of the HFP and LFP lines (Lutz et al., 2017), but SNPs were not related to the 5-HT system. In 9
commercial lines, however, SNPs were found in regions of the HTR2C (encoding 5-HT2C receptor), MAO-A and IL-19 genes in relation to feather damage (Biscarini et al., 2010). Another study in the FP selection lines showed that most SNPs in relation to FP where found on chromosome 4 where the HTR2C gene is located, followed by chromosome 3 where the HTR1B gene is located (Grams et al., 2015). Feather damage was also associated with an unfavorable high allele frequency for the HTR2C gene in birds being severely feather pecked and cannibalized. Similar results were obtained by Yao et al. (2017) where SNPs and enhanced gene expression for HTR2C were related to high feather damage in a Chinese layer line. However, these results were not supported by a recent genome wide association study of Lutz et al. (2017) in relation to performing FP. The results on the 5-HT2C receptor appear to reflect a predisposition for being feather pecked rather than on performing FP. Overall, these genetic studies show that FP is associated with changes in sequence and expression of genes encoding receptors and metabolic enzyme of 5-HT, and the immune system in selection lines as well as in commercial hybrids.

4. Central serotonin, metabolite and turnover levels in birds with diverging pecking tendency

When identifying differences in the central serotonergic system between birds with diverging pecking tendency, studies measure levels of central 5-HT, 5-HIAA and 5-HT turnover (5-HIAA/5-HT) in various brain areas. 5-HIAA is used to reflect MAO-A activity (Wolf et al., 1985) and 5-HT turnover is used as an indicator for activity of the central serotonergic system (Kops, 2014). 5-HT derived from punched tissue are said to reflect metabolic activity of afferent raphe 5-HT fibers and thereby parallels fiber density (Hale and Lowry, 2011), and gives some indication on the storage level of 5-HT. However, levels of 5-HT derived from punched tissue do not provide specific information where in the neuronal system (cell body or synaptic cleft) these levels were measured and it provides no information on the actual release of 5-HT. 5-HT from dialysate gives more information on 5-HT tone and release. All studies discussed here were based on the punched method, except Kops et al. (2014) who, as first, used microdialysis in HFP and LFP chickens. In general, laying hen lines with a high tendency to develop FP show low central 5-HT turnover in multiple brain areas at young age, but at adult age central 5-HT turnover was high in specific brain areas compared to laying hen lines with a low tendency to develop FP (see Table 1). Levels of 5-HT, 5-HIAA and 5-HT turnover in relation to FP at adult age appear brain area specific. Several brain areas were studied to identify differences in the central serotonergic system between birds with diverging pecking tendency, namely the dorsal thalamus (dT) involved in goal-directed behavior (van den Heuvel et al., 2010), medial striatum (mSt) involved in reward (Aoki et al., 2006b), hippocampus (Hpc) involved in memory and learning (Colombo and Broadbent, 2000), hypothalamus (Hyp) involved in the stress response (Puglisi-Allegra and Andolina, 2015), archistriatum (Arch) which includes the arcopallium (Ap) and amygdala (Am) (Reiner et al., 2004) both involved in emotional processes mainly including fear-related behavior (Am) and somatomotor regulation (Ap) (Saint-Dizier et al., 2009), caudo-lateral nidopallium (NCL) and caudo-central nidopallium (NCC) involved in motor actions and decision making (Güntürkün, 2005; Jarvis et al., 2013; Reiner et al., 2004) and the raphe nuclei (RN) a portal for afferent 5-HT neurons (Adell et al., 2002).

4.1. Central serotonin, metabolite and turnover levels in young birds

Only three studies compared central 5-HT activity in laying hen lines which diverge in FP tendency at a young age. van Hierden et al. (2002) examined differences in central 5-HT in young birds from a line selected on egg production traits which diverged in FP behavior, resulting in high (HP) and low pecking (LP) lines (Korte et al., 1997). At 4 weeks of age, HP chicks had lower 5-HT turnover and tended to have lower SHIAA, but higher 5-HT in the rostral brain compared to LP chicks (van Hierden et al., 2002). At 7 weeks of age, HP chicks had lower 5-HIAA (Arch) and tended to have lower 5-HT turnover (forebrain and Arch) and 5-HT (forebrain) compared to LP chicks (van Hierden et al., 2004b). Kops et al. (2017) studied HFP and LFP lines at 8 weeks of age in seven brain areas. HFP chicks had lower 5-HT turnover (Ap, mSt and NCC), 5-HIAA (Am, dT, mSt, and NCC) and 5-HT (dT), and compared to LFP chicks, but no line differences were found in levels of 5-HT turnover, 5-HIAA, 5-HT in the NCL and Hpc (Kops et al., 2017).

4.2. Central serotonin, metabolite and turnover levels in adult birds

At an adult age, multiple studies compared 5-HT levels in brains of birds which diverge in pecking behavior. Namely, comparing HFP with LP line (Kops et al., 2017), feather peckers with non-peckers (Kops et al., 2013a), a control line (CL) with a line selected on low group mortality due to cannibalism (LML; low mortality line) (Kops et al., 2013b), White leghorn (WL) with Rhode Island Red (RIR) (Uitdehaag et al., 2011), and LGPS, HGPS with the commercial hybrid Dekalb XL...
Overall, line or phenotype comparisons did not show differences in 5-HT levels in any brain area measured, except for WL birds that tended to have lower 5-HT in the rostral brain compared to RIR birds (Uitdehaag et al., 2011), and for HFP birds which had higher extracellular 5-HT in the NCC and NCL compared to LFP birds (Kops et al., 2014). For 5-HIAA, birds with high pecking tendency generally had higher levels in the dT (feather pecker vs. non-pecker), mSt (feather pecker vs. victim (Kops et al., 2013a)), Ap (HFP vs. LFP and CL vs. LML (Kopset al., 2017, 2013b)) and the rostral brain (WL vs. RIR (Uitdehaag et al., 2011)) compared to birds with low pecking tendency. 5-HT turnover was higher for birds with high pecking tendency in NCC (HFP vs. LFP (Kops et al., 2017)), dT (feather pecker vs. non-pecker (Kops et al., 2013a)), and in the rostral brain (WL vs. RIR (Uitdehaag et al., 2011)) compared to birds with low pecking tendency. Apart from DXL

| Comparison                              | Age (weeks) | Brain area       | 5-HT | 5-HIAA | 5-HT turnover | Reference               |
|-----------------------------------------|-------------|------------------|------|--------|---------------|-------------------------|
| HP vs. LP                               | 4           | Rostral brain    | ↑    | ↓      | ↓             | van Hierden et al., 2002|
| HP vs. LP                               | 7           | Arch             | =    | ↓      | =             | van Hierden et al., 2004b|
|                                          |             | Forebrain        | =    | =      | =             |                         |
|                                          |             | Hpc              | =    | =      | =             |                         |
| HFP vs. LFP                             | 8           | Am               | =    | =      | =             | Kops et al., 2017       |
|                                          |             | Ap               | =    | =      | =             |                         |
|                                          |             | dT               | ↓    | ↓      | =             |                         |
|                                          |             | Hpc              | =    | =      | =             |                         |
|                                          |             | mSt              | =    | =      | =             |                         |
|                                          |             | NCC              | =    | =      | ↑             |                         |
|                                          |             | NCL              | =    | =      | =             |                         |
| HFP vs. LFP                             | 23          | NCC + NCL        | ↑    | =      | =             | Kops, 2014; Kops et al., 2014|
| HFP vs. LFP                             | 25          | Am               | =    | =      | =             |                         |
|                                          |             | Ap               | =    | =      | =             |                         |
|                                          |             | dT               | =    | ↑      | ↑             |                         |
|                                          |             | Hpc              | =    | =      | =             |                         |
|                                          |             | mSt              | =    | =      | =             |                         |
| Severe feather pecker vs. non-pecker    | 33          | Ap               | =    | =      | =             | Kops et al., 2013a      |
|                                          |             | dT               | =    | =      | =             |                         |
|                                          |             | Hpc              | =    | =      | =             |                         |
|                                          |             | mSt              | =    | =      | =             |                         |
| Severe feather pecker vs. victim        | 33          | Ap               | =    | =      | =             | Kops et al., 2013a      |
|                                          |             | dT               | =    | =      | =             |                         |
|                                          |             | Hpc              | =    | =      | =             |                         |
|                                          |             | mSt              | =    | =      | =             |                         |
| Victim vs. non-pecker                   | 33          | Ap               | =    | =      | =             | Kops et al., 2013a      |
|                                          |             | dT               | =    | =      | =             |                         |
|                                          |             | Hpc              | =    | =      | =             |                         |
|                                          |             | mSt              | =    | =      | =             |                         |
| CL vs. LML                              | 33          | Ap               | =    | =      | =             | Kops et al., 2013b      |
|                                          |             | dT               | =    | =      | =             |                         |
|                                          |             | Hpc              | =    | =      | =             |                         |
|                                          |             | mSt              | =    | =      | =             |                         |
| WL vs. RIR                              | 47          | Rostral brain    | ↑    | ↑      | ↑             | Uitdehaag et al., 2011  |
| DXL vs. HGPS                            | 58          | Hyp              | =    | =      | =             | Cheng and Fahey, 2009   |

Abbreviations for neurotransmitters: 5-HT : 5-hydroxytryptamine, serotonin; 5-HIAA : 5-hydroxyindoleacetic acid; 5-HT turnover : 5-HIAA /5-HT; = : similar levels i.e. no difference; ↑ : increase in levels; ↓ : decrease in levels; * : extracellular concentration measured with microdialysis, " extracellular turnover was determined in the thesis of Kops, 2014, but not used in the published paper Kops et al., 2014; ^ : tendency 0.1 < P > 0.05. Cells in grey : represents birds younger than 10 weeks of age. Cells in white : represents birds older than 20 weeks of age. Abbreviations for comparison: HP : high pecking line; LP : low pecking line (selection on egg production, Korte et al., 1997); HFP : high feather pecking line; LFP : low feather pecking line (selection on feather pecking, Kjaer and Sørensen, 2002); CL : control line for LML; LML: low mortality line (selection on low group mortality, Ellen et al., 2008); WL: white leghorn; RIR : Rhode Island Red; DXL : DeKalb XL; HGPS: high group productivity and survivability line (selection on group productivity and survivability, Cheng and Fahey, 2009). Abbreviations for brain areas (and functions): Am : amygdala (emotion); Ap : arcopallium (somato-motor); Arch : archistriatum (includes Am and Ap); dT : dorsal thalamus (goal-directed behavior); Hpc : hippocampus (memory and learning); Hyp : hypothalamus (stress response); mSt : medial striatum (reward); NCC : caudocentral nidopallium (motor actions and decision making); NCL: caudolateral nidopallium (executive functions and planning); RN : raphe nuclei (afferent); rostral brain and forebrain (various).
birds which had lower 5-HT turnover in the RN compared to HGPS birds (Cheng and Fahney, 2009).

In the FP selection lines, results regarding FP and 5-HT at an adult age seem opposite to what was found at a young age (see Table 1). All differences between the HFP and LFP lines at a young age regarding 5-HT, 5-HIAA or 5-HT turnover in the Am, Ap, dT, mSt and NCC were not found or were opposite at an adult age (Kops et al., 2017). This contradiction in results between young and adult age can be due to the performance of FP at adult age. For example, in the HFP and LFP lines, FP started at 11 weeks of age, after measurements at young age (i.e. 8 weeks of age) but prior to measurements at adult age (i.e. 25 weeks of age) (Kops et al., 2017). Feather pecking as well as receiving FP can influence levels of 5-HIAA and 5-HT turnover, especially in the dT and mSt. Namely, feather peckers have higher 5-HIAA and 5-HT turnover in the dT compared to non-peckers, and higher 5-HIAA in the mSt compared to victims. While victims had higher 5-HIAA and 5-HT turnover compared to non-peckers in the dT, but lower 5-HT and 5-HIAA in the mSt (Kops et al., 2013a).

When measuring extracellular 5-HT and 5-HIAA in the NCC and NCL, HFP birds had higher 5-HT tone, but with no difference in 5-HIAA compared to LFP birds at 23 weeks of age (Kops et al., 2014). In birds that developed FP higher levels of basal extracellular 5-HT indicate changes within the neuronal cell, which could be due to a change in sensitivity of the somatodendritic 5-HT1A autoreceptor or other 5-HT receptors which influence the release of 5-HT. Differences between dialysate and punched tissue measurements in these lines can further direct to extracellular or intracellular mechanisms, respectively. Punched tissue measurements more likely gives information on intracellular processes, while microdialysis gives more information on extracellular processes. Measuring efflux of extracellular 5-HT in specific brain areas (as done by Kops et al., 2014) prior to and during FP could indicate consequences of performing FP on central 5-HT activity. However, ethical considerations and practical feasibility of microdialysis in a social setting where FP could occur has limited this research venue so far. Pharmacological treatments that affect intra- or extracellular processes could be used as an approach to identify where in the synapse or system alterations occur during and after FP has developed.

In summary, at a young age laying hen lines with a high FP tendency had low levels of 5-HT, 5-HIAA or 5-HT turnover in several brain areas (Am, Ap, dT, ventral striatum, mSt, NCC and rostral brain) compared to lines with a low FP tendency (Kops et al., 2017; van Hierden et al., 2004b). The brain areas where low activity was seen are part of the network involved in regulating motor actions and decision making by integrating sensorimotor, motivational and emotional information (Güntürkün, 2005; Jarvis et al., 2013; Reiner et al., 2004). A deficient serotonergic system in these specific brain areas at a young age appears predisposing in the development of FP.

At an adult age, hens originating from lines with a high tendency to develop pecking directed to group mates (FP, toe pecking, cannibalism) showed increased levels of 5-HT, 5-HIAA or 5-HT turnover in the Ap, NCC, NCL and rostral brain compared to hens from lines with a low tendency to develop pecking directed to group mates (Kops et al., 2017, 2014, 2013b; Uitdehaag et al., 2011). These brain areas are involved in motor actions, decision making and fear-related behavior (Güntürkün, 2005; Jarvis et al., 2013; Reiner et al., 2004; Saint-Dizier et al., 2009). Many studies have linked FP to fearfulness (Rodenburg et al., 2004b) and motor activity (Kjaer, 2009), indicating that high 5-HIAA or 5-HT turnover in these specific brain areas at adult age supports FP behavior. Interestingly, feather peckers were found to have a high activity of the serotonergic system in the dT and mSt compared to non-peckers and victims (Kops et al., 2013a), indicating that a high activity of the serotonergic system in these brain areas could be related to the actual performance of FP. The dT and mSt are involved in goal-directed behavior and reward (Aoki et al., 2006b; van den Heuvel et al., 2010), suggesting that the performance of FP could be rewarding. The changes in 5-HT activity (mainly shown by metabolism and turnover) in FP birds (young vs. adult) indicate brain region specific alteration in 5-HT activity. For both young and adult FP chickens, 5-HT metabolism and turnover were affected in the Ap and mSt, and are considered areas as pathways for executive control (Matsushima et al., 2008). Interestingly, in chickens, lesions of the Vst (ventral striatum; containing mSt and nucleus accumbens (NAc)) do not affect cost-dependent foraging choices, while lesions of the Ap do (Aoki et al., 2006a, 2006b). Further, in chickens’ lesions in the Vst cause impulsive choices after a learned paradigm while lesions in the Ap did not affect impulsivity (Izawa et al., 2003; Matsushima et al., 2008). This indicates disassociated functions between the Ap and Vst, and a potential role for site-specific 5-HT influence on impulsivity and foraging in chicken. In chickens, Ap is an important modulator for reward anticipation and foraging choices (Aoki et al., 2003), while the Vst facilitates executive control of behavior dependent on memory-based decision making (Matsushima et al., 2008). All brain regions where 5-HT activity was affected (either 5-HT levels, metabolites or turnover) in FP birds (Am-Ap-mSt-dT-Hpc) are part of a neural network involved in executive cognitive control of foraging behavior (Izawa et al., 2003) and social decision making (O’Connell and Hofmann, 2011). Alterations in 5-HT activity in this network can thus influence different behaviors, as seen in FP birds, such as anxiety, motor activity, stress response and foraging decisions.

5. Where in the serotonergic system of feather pecking birds does it go wrong?

5.1. Serotonin synthesis

Tryptophan is used for synthesis of central 5-HT in the RN and for the synthesis of peripheral 5-HT in EC cells (Coates et al., 2017). Serotonin levels, both central and peripheral, can be influenced by TRP availability and enzymatic activity of TPH. TRP availability is influenced by TRP metabolism via the kynurenine pathway (O’Mahony et al., 2015). Transportation of TRP across the blood-brain-barrier (BBB) via the large amino acid transporter can further influence central 5-HT synthesis. Here, TRP competes with other large neutral amino acids (LNAA). Thus, the TRP/LNAA ratio reflects TRP availability for transportation across the BBB (Fernstrom and Wurtman, 1972). TRP levels and TRP/LNAA ratios in plasma did not differ between lines with high or low FP tendency (HP vs. LP: (7 weeks) van Hierden et al. (2004b); HFP vs. LFP: (17 weeks) Kops et al. (2014); (31 weeks) Buitenhuis et al. (2006)). These findings suggest that TRP availability and availability of TRP for transport across the BBB might not be factors that dysregulate the serotonergic system and thus might not affect FP. However, Kops (2014) found that HFP birds tended to have lower TRP levels compared to LFP birds. This indicates that HFP birds had less TRP available for 5-HT synthesis which could explain the lower central 5-HT activity found in several brain regions compared to LFP birds at a young age (Kops et al., 2017, 2014).

Two ways to identify whether 5-HT synthesis is affected are via ATD or TRP supplementation. Up to now, effects of ATD on FP are still unpublished, although research is ongoing. Birkl et al. (2017b) showed that ATD can decrease TRP levels by 50% and TRP/ (PHE + TYR) ratios by 73% in the plasma of adult HFP birds. Further, feather peckers of the HFP and LFP lines are said to react more strongly on ATD treatment by 73% in the plasma of adult HFP birds. Further, feather peckers of the HFP and LFP lines are said to react more strongly on ATD treatment by 73% in the plasma of adult HFP birds. Further, feather peckers of the HFP and LFP lines are said to react more strongly on ATD treatment by 73% in the plasma of adult HFP birds. Further, feather peckers of the HFP and LFP lines are said to react more strongly on ATD treatment by 73% in the plasma of adult HFP birds. Further, feather peckers of the HFP and LFP lines are said to react more strongly on ATD treatment by 73% in the plasma of adult HFP birds.
in the Hpc. HP chicks which received TRP supplementation showed less gentle FP but more feeding and walking compared to control HP chicks. TRP-supplemented LP chicks showed more foraging but less feeding compared to control LP chicks (van Hieren et al., 2004b). TRP supplementation, via its effect on the serotonergic system in specific brain regions, appears to have affected the behavior of HP and LP chicks differently. This could indicate that birds with high FP tendency may have a more sensitive serotonergic system, especially in brain regions that regulate somato-motor and motivational responses (see Table 1). Overall, TRP supplementation seems to reduce FP behavior, likely via increasing 5-HT levels in these specific brain regions. Savory et al. (1999) showed similar findings in bantams where TRP supplementation resulted in less pecking damage compared to the control treatment, indicating reduced FP in the TRP treated group.

The activity of the rate limiting enzyme TPH could further affect 5-HT synthesis (Walther et al., 2003) and thereby influence FP. Indeed, Wysoki (2007) found that Lohmann Selected Leghorns (high incidence of FP) had lower TPH2 gene expression (encoding tryptophan hydroxylase 2) compared to Lohmann Browns (low incidence of FP). This could indicate reduced TPH activity in lines with a high FP tendency. For instance, mice lacking the gene encoding for brain TPH2, were depleted of brain 5-HT and exhibited an excess of compulsive, aggressive and motor-impulsive behaviors (Angoa-Perez et al., 2012), supporting a potential role for TPH in FP.

In summary, a reduced 5-HT synthesis, potentially due to low TRP availability and/or reduced TPH activity may influence FP. Whether a low TRP availability and/or low TPH activity lies at the heart of FP remains elusive as there are discrepancies between studies and no evidence that SERT plays a role in FP. Unfortunately, there is no direct measurement of SERT in relation to FP. SERT activity can be measured in rodents (Yubero-Lahoz et al., 2013). Kops et al. (2014) injected D-fenfluramine, which induces 5-HT release and blocks 5-HT reuptake by reversing SERT-mediated 5-HT transport (Skelin et al., 2010). Post-injection of D-fenfluramine, HFP and LFP birds had similar 5-HT and 5-HIAA in the NCC and NCL. The lack of difference in extracellular 5-HT and 5-HIAA post D-fenfluramine injection rules out SERT involvement in causing a deficient serotonergic activity in HFP birds in the NCC and NCL. Thus, to date there is no clear evidence that SERT plays a role in FP.

In pigs, a polymorphism in the SERT gene (SLC6A4) has been related to aggression (Terenina et al., 2012), but it is unknown if SERT is related to tail biting, a damaging maladaptive behavior similar to FP (Brunberg et al., 2016). Addressing the influence of SERT directly by use of SSRIs in chickens could help to better understand its role in FP. However, despite the finding that human and chicken SERT are comparable in kinetics and amino acid profile, the affinity of chicken SERT to specific SSRIs is much lower (Larsen et al., 2004). Larsen et al. (2004) showed that the SSRI Fluvoxamine and DASB have high pharmacological affinity in chicken and could thus be used to disentangle the role of SERT in FP.

5.3. Serotonin metabolism

Metabolism of 5-HT can take place in cell bodies, terminals, astrocytes and glial cells by MAO-A and MAO-B. In the terminals, metabolism takes place exclusively via MAO-B, while in cell bodies, astrocytes and glial cells MAO-A and MAO-B are expressed. 5-HT metabolism mostly takes place via MAO-A. MAO-A activity is reflected by metabolite 5-HIAA levels. In the HFP line the MAO-A gene was found to be downregulated compared to the LFP line (Wysoki et al., 2013), indicating that MAO-A activity is reduced in the HFP line. However, adult HFP and LFP birds do not differ in extracellular 5-HIAA post D-fenfluramine injection indicating similar metabolite activity in the NCC and NCL (Kops et al., 2014). But, in two lines predisposed to develop FP, lower 5-HIAA was found at a young age (Kops et al., 2017; van Hieren et al., 2002). These findings can point to a low activity of MAO-A. Yet, at adult age the opposite was found. When comparing HFP vs. LFP (Kops et al., 2017), LML vs. CL (Kops et al., 2013b), WL vs. RIR (Uitdehaag et al., 2011) and feather peckers vs. non-peckers (Kops et al., 2013a), birds with a high tendency to develop FP (HFP, CL, WL and feather peckers) show higher 5-HIAA in several brain areas (Ap, dT, nSt, rostral brain).

In sum, lower MAO-A activity seems to be predisposing in young chicks, while higher MAO activity occurs in birds that already peck. Similarly, tail biting pigs had higher 5-HIAA in their prefrontal cortex compared to victims (Valros et al., 2015). These results further corroborate our suggestion that 5-HT metabolism is involved in damaging behaviors that are directed to conspecifics, such as FP in chickens and tail biting in pigs.

5.4. Serotonin receptors

The 14 families of 5-HT receptors can be found centrally as well as peripherally (for distribution in CNS and peripheral, see Fig. 1, for functions see Coates et al. (2017); Nichols and Nichols (2008)). Pharmacological treatments that act on central 5-HT system can induce or reduce FP and associated behaviors (see Table 2). Most effects on FP have been related to the somatodendritic 5-HT1A autoreceptor. The somatodendritic 5-HT1A autoreceptor has an inhibitory effect on release of 5-HT at the synapse terminals, while other receptors are mainly excitatory (Meguid et al., 2000). Activity of the somatodendritic 5-HT1A autoreceptor controls firing and excitability of 5-HT neurons (Rojas and Fiedler, 2016), and is key to 5-HT tone modulation in 5-HT neurons. At terminals of 5-HT neurons where somatodendritic 5-HT1A autoreceptor are not present, other receptors such as 5-HT1B inhibit 5-HT release. Especially in the mSt 5-HT1B functions as an autoreceptor located at the axon terminal, while in the Hyp 5-HT1B functions as postsynaptic receptor (Adell et al., 2002). Furthermore, agonists of 5-HT2A and 5-HT2C reduce electrical activity of 5-HT neurons, as indicated by reduction of extracellular 5-HT levels at terminals in the RN and also via other neurons (Fink and Göhert, 2007). The chicken brain contains a high density of 5-HT fibers in the Ap and Am and moderate density of 5-HT fibers in the basal ganglia and Hpc (Metzer et al., 2002). The mSt (together with the NAc) previously named the lobus parolfactorius (LPO; Reiner et al., 2004) also shows extremely high innervation of 5-HT, while the NAc is mentioned as having near absence of 5-HT fibers (Metzer et al., 2002). The NAc is involved in reward (Aoki et al., 2006b) and highly DA innervated as well (Kienzel et al., 2011; Mezey and Cillag, 2002). The NAc described by Metzer...
Pharmacological treatments acting on serotonin receptors and the effects on behavior, central serotonin, dopamine, their metabolites and turnovers in chickens.

Table 2

| Treatment | Action | Lines | Age at treatment | Age at measurement | Behavior effect | Brain area | 5-HT | 5-HIAA | 5-HT turnover | DA | DOPAC | HVA | DA turnover | Reference |
|-----------|--------|-------|------------------|-------------------|-----------------|-----------|------|--------|--------------|----|--------|------|-----------|-----------|
| 5-HT      | Elevate 5-HT | WL    | incubation day 1 | 1d, 15d, 30d, 9w, 18w | 5-HT | Hpc, RN | ↑15d | ↓18w | ↓18w | ↓18w | ND | ND | ND | ND | Dennis et al., 2013a |
| 5-OH-DPAT | 5-HT1A antagonist | WL    | first 2 days | 5-HT | Hpc, RN | ND | ND | ND | ND | ND | ND | ND | ND | Dennis et al., 2013b |
| TRP       | Elevate TRP | Local breed | 3d | 5d | 5-HT | ND | ND | ND | ND | ND | ND | ND | ND | Zendeheil et al., 2017 |
| Fluoxetine | SSRI | WL | 8-11d | 5-HT | ND | ND | ND | ND | ND | ND | ND | ND | ND | Matsuura et al., 2012 |
| 5-OH-DPAT | 5-HT1A antagonist | Local breed | 3w | 3w for 4h | 5-HT | ND | ND | ND | ND | ND | ND | ND | ND | Zendeheil et al., 2012 |
| SB 242084 | 5-HT2C antagonist | HP, LP | 4w | 4w | 5-HT | HP | Arch, Forebrain | ND | ND | ND | ND | ND | ND | ND | van Hierden et al., 2004a |
| NAM-190 | Auto 5-HT1A agonist, Post 5-HT1A antagonist | LGPS, DIXL, HGPS | 24w for 5d | 24w for 5d | 5-HT | HP, LGPS & DIXL | ND | ND | ND | ND | mHSP | mHSP | ND | Dennis et al., 2012; Dennis and Cheng, 2012 |
| GR-127935 | 5-HT1B antagonist | HP, LGPS & DIXL | ND | ND | 5-HT | HGPS | ND | ND | ND | ND | mHSP | mHSP | ND | ND | Dennis et al., 2012; Dennis and Cheng, 2012 |

Abbreviation for treatment effects: 5-HT: 5-hydroxytryptamine, serotonin; 5-HIAA: 5-hydroxyindoleacetic acid; 5-HT turnover: 5-HIAA /5-HT; DA: dopamine; DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; DA turnover: metabolites (HVA, DOPAC)/DA; =: similar levels i.e. no treatment effect; ↑: increase after treatment; ↓: decrease after treatment; when lines are expressed: indicates treatment effect within specific line; ND: not determined; *: extracellular concentration measured with microdialysis; #: tendency 0.1 < P > 0.05. Cells in grey: represents birds younger than 10 weeks of age. Cells in white: represents birds older than 20 weeks of age. Abbreviations for ages: d: days; w: weeks; h: hours; min: minutes. Abbreviations for behaviors: aggr: aggression; TI: tonic immobility duration (fear response); FP: feather pecking. Abbreviations for brain areas: Arch: archistriatum; Dph: Diencephalon; Hpc: hippocampus; Hpc: hypothalamus; mSt: medial striatum; NCC: caudolateral nidopallium; NCL: caudolateral nidopallium; RN: raphe nuclei.

et al. (2002) however likely refers to the BST (bed nucleus of the stria terminals) as shown by recent anterograde pathway tracing study in chickens (Bálint et al., 2011; Kuenzle et al., 2011). Further, the NAC can be divided in shell and core (Bálint and Csillag, 2007) with different efferent and afferent projections (Bálint et al., 2011). Now looking at the results of the study by Metzger et al. (2002) the NAC core and shell are more likely highly 5-HT innervated. Further, the defined chick’ NAC by (Puelles et al., 2007) is disputed by (Matsushima et al., 2008) and could likely contain a larger caudal area of the mSt (Bálint and Csillag, 2007). Quantification of 5-HT-receptor density in different brain areas and peripherally in relation to FP is unknown.

5.4.1. Pharmacological treatments acting on serotonin receptors in relation to feather pecking

S-15535 and NAN-190 are drugs with agonistic action on the somatodendritic 5-HT1A autoreceptor and thereby reduce 5-HT release and turnover. They further have antagonistic actions on the post-synaptic 5-HT1A receptor, hereby they block or dampen the binding of 5-HT to the post-synaptic 5-HT1A receptor. S-15535 increased FP in HP chicks compared to saline treated HP chicks and reduced 5-HT turnover in the Arch of HP chicks (van Hierden et al., 2004a). NAN-190 induced FP and aggression (Dennis et al., 2008) and decreased 5-HIAA in the RN of the LGPS line, a highly aggressive chicken line (Dennis and Cheng, 2012). In adult hens, GR-127935 (agonist for 5-HT1B receptor) increased FP and aggression also in a less aggressive line (HGPS) but did not affect 5-HT or 5-HIAA levels (Dennis et al., 2008; Dennis and Cheng, 2012). Treatment with 8–OH-DPAT (full agonist for somatodendritic 5-HT1A autoreceptor) at a young age increased fearfulness (Dennis et al., 2013a), but did not affect FP (Korte, personal communication). In other species, agonizing somatodendritic 5-HT1A autoreceptor can aggravate compulsive behaviors (Zohar and Insel, 1987), while inhibiting the somatodendritic 5-HT1A autoreceptor can reduce self-inflicted feather picking in parrots (Bordnick et al., 1994) and stereotypic behavior in voles (Shoeneker and Heller, 2003). These studies show a direct link between the somatodendritic 5-HT1A autoreceptor and malfunctioning motor disruptive behavior (FP and feather picking) as well as maladaptive stereotypic behavior.

5.4.2. Evidence for involvement of the 5-HT1A receptor in feather pecking

There is strong evidence that somatodendritic 5-HT1A autoreceptor functioning is related to FP (pharmacological treatment (van Hierden et al., 2004a) and genetic polymorphisms of DEAF1, repressing transcription of the 5-HT1A gene (Filisikowski et al., 2009)). Deficient functioning of the somatodendritic 5-HT1A autoreceptor and 5-HT2C are associated with impulsivity in rodents (Dalley et al., 2011). Especially action inhibition, the inability to stop an action when it is initiated, has been associated with reduced somatodendritic 5-HT1A autoreceptor functioning (Korte et al., 2017). SSRI treatment, which desensitizes the somatodendritic 5-HT1A autoreceptor and blocks SERT, decreased impulsivity and increased extracellular 5-HT and DA in the mSt of chicks (Matsunami et al., 2012). There are indications that birds with low levels of whole-blood 5-HT (de Haas and Rodenburg, 2016) and HFP birds (Birkl et al., 2016) lack action inhibition in impulsivity tests. HFP birds also react faster and more active to various
behavioral tests at young and adult ages (Kops et al., 2017; Pichova et al., 2017; van der Eijk et al., 2018). These findings together suggest that FP birds appear more impulsive which could be due to a deficient somatodendritic 5-HT1A autoreceptor.

Further, a tendency for low plasma TRP levels in HFP birds can point to deficient functioning of the somatodendritic 5-HT1A autoreceptor (Cahir et al., 2007). Synthesis of 5-HT from TRP is regulated, in part, by the somatodendritic 5-HT1A autoreceptor as it can inhibit 5-HT synthesis via its action on TPH (Best et al., 2010). This receptor might affect 5-HT levels and FP via its effects on TRP availability (as shown by van Hierden et al. (2002)) and injecting NAN-190 in chickens increased plasma TRP (Dennis et al., 2008). Moreover, binding of somatodendritic 5-HT1A autoreceptor in the dorsal raphe of rats is reduced by ATD (Cahir et al., 2007). Therefore, lower levels of TRP in lines with a high pecking tendency could represent a dysregulated somatodendritic 5-HT1A autoreceptor. This dysregulation can reduce 5-HT synthesis from TRP and the termination of 5-HT activity. However, it remains unknown whether alterations in the number, sensitivity and/or density of the somatodendritic 5-HT1A autoreceptor is causing these effects.

5.5. Peripheral serotonin

Peripheral 5-HT plays a role in various physiological functions, such as gut motility, immune regulation, and energy metabolism (Coates et al., 2017). Lines that are prone to peck conspecifics or already developed FP generally have lower whole-blood 5-HT levels compared to neutrals but only at 21 weeks of age and not at 24, 27, 32 or 37 weeks of age (Daigle et al., 2015). A previous study in the FP selection lines found that HFP birds had higher plasma 5-HT levels compared to LFP birds at 31 weeks of age (Buitenhuis et al., 2006). Plasma 5-HT derives mainly from gut 5-HT which has not yet been transported back into platelets or EC cells by SERT (Shajib and Khan, 2015). Whole-blood 5-HT level is more likely reflects the storage concentration of 5-HT, while plasma 5-HT levels are correlated with central 5-HT levels than plasma 5-HT levels (Audhya et al., 2012).

Measurements of peripheral 5-HT uptake can provide indications of peripheral SERT activity. Platelet 5-HT uptake was found to be higher for CL vs. LML hens (Bolhuis et al., 2009; Rodenburg et al., 2009a) and WL vs. RIR at 47 weeks (Uitdehaag et al., 2011) and HFP vs. LFP at 24 weeks of age but not at 14 weeks of age (van der Eijk et al., 2017, unpublished results). Feather pecker-victims and victims of a White shaver line also had lower whole-blood 5-HT levels compared to neutrals but only at 21 weeks of age and not at 24, 27, 32 or 37 weeks of age (Daigle et al., 2015). A previous study in the FP selection lines found that HFP birds had higher plasma 5-HT levels compared to LFP birds at 31 weeks of age (Buitenhuis et al., 2006). Plasma 5-HT derives mainly from gut 5-HT which has not yet been transported back into platelets or EC cells by SERT (Shajib and Khan, 2015). Whole-blood 5-HT levels are more likely reflects the storage concentration of 5-HT, while plasma 5-HT levels are more correlated with central 5-HT levels than plasma 5-HT levels (Audhya et al., 2012). Whole-blood 5-HT level is more likely reflects the storage concentration of 5-HT, while plasma 5-HT levels are more correlated with central 5-HT levels than plasma 5-HT levels (Audhya et al., 2012).

Measurements of peripheral 5-HT uptake can provide indications of peripheral SERT activity. Platelet 5-HT uptake was found to be higher for CL vs. LML hens (Bolhuis et al., 2009; Rodenburg et al., 2009a) and WL vs. RIR birds (Uitdehaag et al., 2011), but no studies on platelet 5-HT uptake in relation to FP phenotypes have been conducted. In adult

Table 3
Peripheral serotonin in birds with diverging pecking tendency.

| Comparison | Age (weeks) | Whole-blood 5-HT uptake | Reference |
|------------|-------------|--------------------------|-----------|
| HFP and LFP vs. CON | 14 | ↓ | ND | van der Eijk et al., unpublished results |
| DW vs. ISA Brown | 15 | ↓ | ND | de Haas et al., 2014a |
| Feather pecker vs. neutral | 21 | = | ND | |
| Feather pecker vs. victim | 24, 27 | = | ND | Daigle et al., 2015 |
| Feather pecker vs. feather pecker-victim | = | = | |
| Feather pecker-victim vs. victim | = | = | Daigle et al., 2015 |
| Feather pecker-victim vs. neutral | = | = | |
| Victim vs. neutral | = | = | |
| HFP vs. LFP and CON | 24 | ↓ | ND | van der Eijk et al., 2017a |
| CL vs. LML | 29 | ↑ | ↑ | Bolhuis et al., 2009 |
| WL vs. RIR | 47 | ↓ | ↑ | Uitdehaag et al., 2011 |
| DNL vs. HGPS | 58 | = | ND | Cheng and Fahey, 2009 |

Abbreviations for measurements: 5-HT: 5-hydroxytryptamine, serotonin; =: similar levels i.e. no difference; ↑: increase in levels; ↓: decrease in levels; p: measured in plasma; *: interaction brooding by surrogate hen. Cells in grey: represents birds younger than 20 weeks of age. Cells in white: represents birds older than 20 weeks of age. Abbreviations for comparison: DW: Dekalb White, commercial cross of White leghorn; ISA Brown: commercial cross of Rhode Island Red; HFP: high feather pecking line; LFP: low feather pecking line; CON: unselected control line of the FP selection lines (selection on feather pecking, Kjaer and Sørensen, 2002); CL: control line for LML; LML: low mortality line (selection on low group mortality, Ellen et al., 2008); WL: white leghorn; RIR: Rhode Island Red; DXL: DeKalb XL; HGPS: high group productivity and survivability line (selection on group productivity and survival, Cheng and Fahey, 2009).
hens, a positive correlation between whole-blood 5-HT and central 5-HT in the rostral brain have been found irrespective of line or social environment, and between platelet 5-HT turnover and central 5-HT turnover (rostral brain) within the W line (Uttenthal et al., 2011). These findings give rise to the suggestion that platelet 5-HT activity is related to central 5-HT activity, although research is needed to assess these relations by taking into account brain area and age at measurement. As in tail-biting pigs the correlation between whole-blood and central 5-HT measurements are dependent on age (Ursinus et al., 2013) and brain area (Valros et al., 2015). Up to now, it is unknown whether peripheral 5-HT (plasma, whole blood or platelet uptake) is affected in young birds predisposed to develop FP. It would be interesting to identify peripheral 5-HT in birds prior to and after the development of FP. With this information it would be possible to assess cause and effect of peripheral 5-HT on FP. Although central and peripheral 5-HT act independently, they can also interact via the bloodstream as affected by the immune system and gut microbiota (GM; microflora of the intestine).

5.5.1. Interaction between the serotonergic system, immune system and feather pecking

Serotonin receptors and the 5-HT transporter are distributed on various immune cells. Peripheral 5-HT has several functional roles in the immune system for example, it is required for optimal functioning of monocytes and macrophages, it is important for natural immunity delivered by macrophages (Mössner and Leisch, 1998), and plays an important role in the gut inflammation response (O’Mahony et al., 2013). In birds, peripheral 5-HT is released by macrophages in response to infection and plays an important role in the gut inflammation response (O’Mahony et al., 2013). For example, in broilers, TRP supplementation helped to maintain the intestinal barrier, increased plasma 5-HT and reduced TPH expression (Yue et al., 2017). In turn, the immune system can influence the serotonergic system as well. Cytokines, the key signaling molecules of the immune system (Kaiser and Stäheli, 2014), influence the synthesis, re-uptake and release of 5-HT (Anisman and Merali, 2002; Karrenbauer et al., 2011; Miller et al., 2013). For example, inflammatory cytokines activate indoleamine 2,3 dioxygenase the enzyme that converts TRP into kynurenine, hereby reducing TRP availability for 5-HT synthesis (Dantzer et al., 2008). Further, Tumour Necrosis Factor and IL-1 increase SERT activity in the midbrain and mSt of mice (Zhu et al., 2006). The immune system might affect FP via its influence on central and peripheral 5-HT. Indeed, several studies found a relation between the immune system and FP; by associations between feather damage and cytokine genes (IL-9, IL-4) (Biscarini et al., 2010), by upregulation and downregulation of genes involved in immune responses in feather pecking birds (Brumberg et al., 2011), by genetic associations between FP and total antibody response (Buitenhuys et al., 2003), and by a specific immune challenge as young and increased feather damage as adult (Parmentier et al., 2009). In the FP selection lines, HFP birds showed a higher antibody response to Infectious Bursal Disease Virus vaccination, while LFP birds showed more leukocytes and higher expression of MHC class I molecules on T (CD4, CD8) and B cells (Buitenhuys et al., 2006). Indicating that HFP and LFP birds differ in immune competence. Whether the relation between FP and the immune system occurs via, or affects the serotonergic system remains to be proven.

5.5.2. Interaction between the serotonergic system, gut microbiota and feather pecking

Gut 5-HT is an important signaling molecule regulating gastrointestinal motor, secretory and sensory functions (Kezethelyi et al., 2009; Lesuret et al., 2008). Another peripheral factor which can influence both peripheral and central 5-HT is the GM. GM can activate cytokines (Bauer et al., 2006; Sommer and Bäckhed, 2013), which can influence central 5-HT release, as described above. Specific GM utilize or produce TRP (Zhang and Davies, 2016) and thereby influence TRP availability for 5-HT synthesis. Plasma TRP is increased in Bifidobacterium infantis treated rats (Desbonnet et al., 2008). Also 5-HT turnover (mSt) was higher in germ-free mice which lack a GM (Heijtz et al., 2011) and 5-HIAA (frontal cortex) was reduced in probiotics treated mice (Desbonnet et al., 2008). GM also produce SCFA involved in neurotransmitter synthesis and release (DeCastro et al., 2005; Shah et al., 2006), such as butyrate, acetate and propionate that can cross the BBB (Oldendorf, 1973). Oral treatment with propionate shows to lower 5-HT in the entire rat brain (El-Ansary et al., 2012). GM can further influence central 5-HT release via the vagus nerve (Bercik et al., 2011; Bravo et al., 2011). In rodents, GM composition has been shown to influence various behaviors, such as emotionality, sociality and cognition (Collins et al., 2012; Cryan and Dinan, 2012). GM composition could potentially influence FP via its effects on central and peripheral 5-HT. HFP and LFP lines differ in microbiotal metabolites, the products of GM, with HFP birds having more propionate and butyrate compared to LFP birds (Meyer et al., 2013). Preliminary results show that these FP selection lines also tended to differ in GM composition at 30 weeks of age (van der Eijk et al., 2017b). However, whether a specific GM composition is causal in FP remains to be proven. It is plausible that the differences in GM composition and metabolites in the FP selection lines is caused by eating feathers. Adding feathers to diet has been shown to alter GM and increases propionate and butyrate in hens (Meyer et al., 2012). HFP birds often ingest feathers, work to obtain freely available feathers (Harlander-Matauschek et al., 2007) and like foraging in feathers (McKeegan and Savory, 1999). Eating loose feathers also often precedes FP (de Haas et al., 2014a). Some authors have suggested that FP and eating feathers may be a way to compensate for the lack of central 5-HT (Kops et al., 2017). Ingestion of feathers may cause 5-HT release in the gut. Gut 5-HT namely reacts on sensory perception of the mucosal layer (Coates et al., 2017). As a consequence of ingesting fibers, large particles or feathers, gut 5-HT can stimulate secretion of signaling mediators. These mediators can potentiate neurons, making them more likely to respond, and influence neuronal action potential (Coates et al., 2017). Peripheral 5-HT may thereby influence neuroplasticity of serotonergic neurons. When chicks are kept on paper remnants and wood shavings (i.e. large particles) in the first weeks of life whole-blood 5-HT at 15 weeks of age was higher compared to chicks that did not have access to substrate (de Haas et al., 2014a). As these birds have the ability to ingest large particles, this could influence gut 5-HT and GM. Interestingly, feeding a high fiber diet tended to increase plasma 5-HT levels compared to feeding a low fiber diet in horses (Alberghina et al., 2006). Eating fibers or feathers might thus increase peripheral 5-HT levels in chickens. Eating feathers may derive from a need for satiety sensation, and thereby playing a causal role in FP (Harlander-Matauschek and Bessei, 2005). For example, feathers in the diet reduced FP and improved plumage condition in hens (Kriegeski et al., 2012). How and if eating feathers affects the serotonergic system in chicken is unknown.

6. The dopaminergic system in relation to feather pecking

Central DA activity is affected in birds with a high FP tendency (see Table 4). As mentioned, central 5-HT is involved in appetite, food intake and satiety. Central DA facilitates the motivation to perform rewarding behavior (De Deurwaerdère and Di Giovanni, 2017). Through their functions, 5-HT and DA could facilitate FP, as a redirected feeding related behavior. Central 5-HT could initiate FP and feather eating and DA could further reinforce this behavior. Rewarding effects of several stimuli (such as feeding behavior) are regulated via DA in the mesolimbic system (De Deurwaerdère and Di Giovanni, 2017). Mesolimbic DA regulates acquisition, control and maintenance of goal-directed behavior (Kiyatkin, 1995). Thus, it is plausible that DA regulates the continuation of FP.
6.1. Genetic associations between the dopaminergic system and feather pecking

Genetic polymorphisms of genes encoding the D4 receptor (DRD4) and influencing transcription of HTR1A via DEAF1 were associated with FP (Flisikowski et al., 2009). The DEAF1 gene also modulates the proenkephalin gene (Huggenvik et al., 1998). Proenkephalin is a component in the dopamine-reward cascade associated with compulsivity (Blum et al., 2000; Bordnick et al., 1994). Compulsive animals appear to be unable to stop their behavior and reflect a stick-in-set perseverance. Stick-in-set perseverance is reflected by impulsivity and compulsivity, and associated with behavioral pathologies in rodents (Garner et al., 2006), TTM in humans (Chamberlain et al., 2006; Fineberg et al., 2010) and self-inflicted feather picking and plucking in parrots (van Zeeland et al., 2009). A recent study, however, found that HFP birds have similar perseverance as LFP birds in a pecking specific task (Kjaer et al., 2015), indicating that FP in these lines might not be related to compulsivity but more to hyperactivity (Kjaer, 2009). Whether continuing to perform FP is related to DA and compulsivity is unknown.

6.2. Dopaminesynthesis

Dopamine is synthesized from its precursor TYR. Dopamine synthesis appears reduced in HFP birds compared to LFP birds, as indicated by lower TYR and PHE in HFP birds (Kops, 2014; Kops et al., 2014). In CL birds aggression was related to DA synthesis as peripheral TRP/(PHE+TYR) ratio was reduced (Birkl et al., 2017a). Furthermore, CL

| Comparison | Age (weeks) | Brain area | DA | DOPAC | HVA | 3-MT | DA turnover | Reference |
|------------|-------------|------------|----|-------|-----|------|-------------|-----------|
| HP vs. LP  | 4           | Rostral brain |    |       |     |      |             | van Hierden et al., 2002 |
| HFP vs. LFP | 8     | Am = = = ND = |    |       |     |      |             | Kops et al., 2017 |
|            |             | Ap = = = ND = |    |       |     |      |             |           |
|            |             | dT = = = ND = |    |       |     |      |             |           |
|            |             | Hpc = = = ND = |    |       |     |      |             |           |
|            |             | mSt = = = ND = |    |       |     |      |             |           |
|            |             | NCC = = = ND = |    |       |     |      |             |           |
|            |             | NCL = = = ND = |    |       |     |      |             |           |
| DXL vs. HGPS | 24 | Hyp = = = ND = |    |       |     |      |             | Dennis and Cheng, 2012 |
|            |             | RN = = = ND = |    |       |     |      |             |           |
| HFP vs. LFP | 25 | Am = = = ND = |    |       |     |      |             | Kops et al., 2017 |
|            |             | Ap = = = ND = |    |       |     |      |             |           |
|            |             | dT = = = ND = |    |       |     |      |             |           |
|            |             | Hpc = = = ND = |    |       |     |      |             |           |
|            |             | mSt = = = ND = |    |       |     |      |             |           |
|            |             | NCC = = = ND = |    |       |     |      |             |           |
|            |             | NCL = = = ND = |    |       |     |      |             |           |
| Severe feather pecker vs. non-pecker | 33 | Am = = = ND = |    |       |     |      |             | Kops et al., 2013a |
|            |             | dT = = = ND = |    |       |     |      |             |           |
|            |             | Hpc = = = ND = |    |       |     |      |             |           |
|            |             | mSt = = = ND = |    |       |     |      |             |           |
| Severe feather pecker vs. victim | 33 | Am = = = ND = |    |       |     |      |             | Kops et al., 2013a |
|            |             | dT = = = ND = |    |       |     |      |             |           |
|            |             | Hpc = = = ND = |    |       |     |      |             |           |
|            |             | mSt = = = ND = |    |       |     |      |             |           |
| Victim vs. non-pecker | 33 | Am = = = ND = |    |       |     |      |             | Kops et al., 2013a |
|            |             | dT = = = ND = |    |       |     |      |             |           |
|            |             | Hpc = = = ND = |    |       |     |      |             |           |
|            |             | mSt = = = ND = |    |       |     |      |             |           |
| CL vs. LML | 33 | Am = = = ND = |    |       |     |      |             | Kops et al., 2013b |
|            |             | dT = = = ND = |    |       |     |      |             |           |
|            |             | Hpc = = = ND = |    |       |     |      |             |           |
|            |             | mSt = = = ND = |    |       |     |      |             |           |
| WL vs. RIR | 47 | Rostral brain = = = = = |    |       |     |      |             | Ulldahaag et al., 2011 |

Abbreviations for neurotransmitters: DA : dopamine; DOPAC : 3,4-dihydroxyphenylacetic acid; HVA : homovanillic acid; 3-MT : 3-methoxytyramine; DA turnover : DOPAC + HVA / DA (for Kops et al., 2017; van Hierden et al., 2002); DOPAC + HVA + 3-MT / DA (for Kops et al., 2013a, 2013b); DOPAC / DA (for Ulldahaag et al., 2011); = : similar levels i.e. no difference; ↑ : increase in levels; ↓ : decrease in levels; bdl : below detection level; ND : not determined; ^ : tendency 0.1 < P > 0.05. Cells in grey: represents birds younger than 10 weeks of age. Cells in white: represents birds older than 20 weeks of age. Abbreviations for comparison: HP : high pecking line; LP : low pecking line (selection on egg production, Korte et al., 1997); HFP : high feather pecking line (selection on feather pecking, Kjaer and Serensen, 2002); DXL : DeKalb XL; HGPS: high group productivity and survivability line (selection on group productivity and survivability, Cheng and Fahey, 2009); CL : control line for LML; LML: low mortality line (selection on low group mortality, Ellen et al., 2008); WL: white leghorn; RIR : Rhode Island Red. Abbreviations for brain areas (functions): Am : amygdala (emotion); Ap : arcopallium (somato-motor); dT : dorsal thalamus (goal-directed behavior); Hpc : hippocampus (memory and learning); Hyp : hypothalamus (stress response); mSt : medial striatum (reward); NCC : caudocentral nidopallium (motor actions and decision making); NCL : caudolateral nidopallium (executive functions and planning); RN : raphe nuclei (afferent); rostral brain (various).
birds had a higher innervation of tyrosine hydroxylase (TH; the rate limiting enzyme for DA synthesis) in the NCC than LML birds (Nordquist et al., 2013). TH innervation reflects development of DA neurons. Thus CL birds with higher aggression and cannibalistic pecking show increased innervation of DA system and higher availability of DA precursors. However, whether the direct precursor of DA, L-3,4-di-hydroxyphenylalanine (L-DOPA,) is affected in birds which are prone to develop FP or perform FP is unknown.

6.3. Central dopamine, metabolites and turnover levels in young birds

At a young age, no differences were found in central DA levels between HP vs. LP and HFP vs. LFP (see Table 4). Also, no differences were found between HFP and LFP birds in DA metabolites (i.e. 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; DA turnover: metabolites/DA (DOPAC, HVA)/DA ; =: similar levels i.e. no treatment effect; ↑: increase after treatment; ↓: decrease after treatment; when lines are noted this indicates treatment effect within that specific line; ND: not determined; *: tendency 0.1 < P > 0.05. Cells in grey : represents birds younger than 10 weeks of age; Cells in white : represents birds older than 20 weeks of age. Abbreviations for lines: HP : high pecking line; LP : low pecking line (selection on egg production, Korte et al., 1997); DXL : DeKalb XL; HGPS: high group productivity and survivability line; LGPS : low group productivity and survivability line (selection on group productivity and survival, Cheng and Fahey, 2009) dom: dominant; sub: subordinate; ISA : ISA Brown. Abbreviations for ages: d : days; w: weeks; h : hours; min : minutes. Abbreviations for behaviors: aggr : aggression; FP : feather pecking. Abbreviations for brain areas: Hyp : hypothalamus; RN : raphe nuclei.

Abbreviations for treatment effects: 5-HT : 5-hydroxytryptamine, serotonin; 5-HIAA : 5-hydroxyindoleacetic acid; 5-HT turnover : 5-HIAA /5-HT; DA : dopamine; DOPAC : 3,4-dihydroxyphenylacetic acid; HVA : homovanillic acid; DA turnover: metabolites/DA (DOPAC, HVA)/DA ; =: similar levels i.e. no treatment effect; ↑: increase after treatment; ↓: decrease after treatment; when lines are noted this indicates treatment effect within that specific line; ND: not determined; *: tendency 0.1 < P > 0.05. Cells in grey : represents birds younger than 10 weeks of age; Cells in white : represents birds older than 20 weeks of age. Abbreviations for lines: HP : high pecking line; LP : low pecking line (selection on egg production, Korte et al., 1997); DXL : DeKalb XL; HGPS: high group productivity and survivability line; LGPS : low group productivity and survivability line (selection on group productivity and survival, Cheng and Fahey, 2009) dom: dominant; sub: subordinate; ISA : ISA Brown. Abbreviations for ages: d : days; w: weeks; h : hours; min : minutes. Abbreviations for behaviors: aggr : aggression; FP : feather pecking. Abbreviations for brain areas: Hyp : hypothalamus; RN : raphe nuclei.

6.4. Central dopamine, metabolites and turnover levels in adult birds

At an adult age, birds with a high pecking tendency had lower DA in rostral brain (WL vs. RIR (Uitdehaag et al., 2011)), NCC (HPF vs. LFP (Kops et al., 2017)) and RN (DXL vs. HGPS (Dennis and Cheng, 2012)) than birds with a low pecking tendency (see Table 4). Apart from CL birds which tended to have higher DA levels in the Ap compared to LML birds (Kops et al., 2013b). Birds with a high pecking tendency had higher metabolite levels of DA in Ap (DOPAC: HFP vs. LFP and CL vs. LML; HVA: feather pecker vs. neutral and CL vs. LML), dT (DOPAC; CL vs. LML), rostral brain (DOPAC: WL vs. RIR) compared to birds with a low pecking tendency (Kops et al., 2017, 2013a, 2013b; Uitdehaag et al., 2011). Apart from HFP birds which had lower DOPAC in the NCC compared to LFP birds (Kops et al., 2017). DA turnover was higher in the NCC for HFP vs. LFP birds and in the rostral brain for WL vs. RIR birds (Kops et al., 2017; Uitdehaag et al., 2011), but lower in the Hpc for CL vs. LML birds (Kops et al., 2013b). Discrepancies between studies might be caused by the calculation of DA turnover - either by DOPAC + HVA/DA (Kops et al., 2017; van Hierden et al., 2002), DOPAC + HVA + 3-methoxytyramine (3-MT)/DA (Kops et al., 2013b) or DOPAC/DA (Uitdehaag et al., 2011) and by inclusion of phenotypes in analysis of genotypes.

In summary, chicks with high FP tendency not only show deficiency in the serotonergic system, but also in the dopaminergic system. Although less brain areas were affected compared to the serotonergic system, lower DA activity was found in brain areas involved in motivation and reward (mSt) and in goal-directed behavior (dT) in chicks with a high FP tendency. These findings suggest that a low activity of the dopaminergic system in these brain areas at a young age is involved in the development of FP. At an adult age, DA activity was higher in a brain region involved in somato-motor actions (Ap), goal-directed behavior (dT) and decision making (NCC) in birds with a high pecking tendency. This indicates high activity of the dopaminergic system in these specific brain areas in the performance of pecking behavior. However, precaution is needed when interpreting these results as findings for the DA system showed more inconsistencies than those for the 5-HT system (see Tables 1 & 4), especially at an adult age. Discrepancies seen between the mortality selection lines, group productivity and survivability lines and FP selection lines might further be explained by the selection criteria. Within the LML and CL lines hardly any FP or feather damage due to FP has been found (Bohlius et al., 2009; de Haas et al., 2012), but CL birds performed more cannibalistic toe pecking than LML birds (Rodenburg et al., 2009a). Similarly, the HGPS, LGPS and DXL lines did not differ in FP (Dennis et al., 2008), but HGPS birds had less feather damage, performed less cannibalistic and aggressive pecking compared to DXL and LGPS birds (Craig and Muir, 1996a, 1996b). Aggressive pecking and FP may be both influenced by DA activity, but specific for the different genetic lines (i.e. having a tendency for more FP, more cannibalism, or more aggression).
6.5. Interaction between the serotonergic and dopaminergic system and the influence on feather pecking

6.5.1. Pharmacological treatments acting on serotonin receptors influencing the dopaminergic system

The serotonergic system can influence brain region-specific DA tone and release by various routes via 5-HT receptors (De Deurwaerdère and Di Giovanni, 2017). It is known that 5-HT receptors can influence DA release from mesolimbic dopaminergic neurons in mammals (Fink and Göthert, 2007). The postsynaptic 5-HT1A receptor is a major modulator for striatal DA activity (De Deurwaerdère and Di Giovanni, 2017), but also 5-HT2 receptors play an important role in DA release in the NAc (De Deurwaerdère and Spampinato, 2001). Also in chicken, explicit roles for the somatodendritic 5-HT1A autoreceptor and postsynaptic 5-HT1B receptor in DA activity have been found (Dennis et al., 2013a). Treatment with NAN-190 decreased DA in the RN of HGPS birds but not in DXL birds (Dennis and Cheng, 2012). When given GR-127935 (5-HT1B and 5-HT1D receptor antagonist) DA decreased and DA turnover increased in the RN of HGPS birds but not in DXL birds (Dennis and Cheng, 2012). In HP chicks the highest dosage of S-15535 enhanced dopamine turnover in the Hpc and Arc, but this effect was not seen in LP chicks (van Hieren et al., 2004a) (see Table 2). Another 5-HT1A agonist (8-OH-DPAT) shows biphasic actions on 5-HT1A receptors in the Hipp of rats. A low dose inhibits 5-HT release by acting on the somatodendritic 5-HT1A autoreceptor and increased DA release, while a high dose also acts strongly on postsynaptic 5-HT receptors and inhibits DA release (Montgomery et al., 1991).

6.5.2. Pharmacological treatments acting on dopamine receptors in relation to feather pecking

Pharmacological treatments that affect the dopaminergic system either reduce or induce pecking behavior (see Table 5). Treatment with a D1 agonist (SKF-38393) increased FP, aggression, 5-HT and 5-HAA levels in RN of subordinate adult hens, while treatment with D1 or D2 antagonist (SCH-23390 and Raclopride, respectively) decreased FP, aggression and increased 5-HT in RN of dominant hens (Dennis and Cheng, 2011). A D2 antagonist (Raclopride) also reduced aggression in highly aggressive birds (Dennis et al., 2006). Thus, D1 and D2 receptors play a role in aggression, likely via their influence on 5-HT levels in the RN. Interestingly, D2 receptor activity is also involved in FP, namely in adult HFP hens, a D2 antagonist (Haloperidol) decreased FP, foraging, walking and eating, but not aggression (Kjaer et al., 2004). These results are likely caused by Haloperidol blocking the effects of DA and increasing frontal and NAc′ DA (Bonaccorso et al., 2002; Li et al., 2005) and increase in overall behavior inhibition (Legemman et al., 2017). When given a D2 receptor antagonist (Haloperidol or Raclopride), all types of pecking behaviors are reduced (Dennis et al., 2006; Goodman, 1981) and specifically FP and not aggressive pecking in HFP birds (Kjaer et al., 2004). Haloperidol also tends to decrease the frequency of foraging when anticipating a food reward (Moe et al., 2014). Further, van Hieren et al. (2005) showed that Apomorphine (full D1 and D2 agonist) in HP chicks increased walking in a novel environment, indicating reduced fear and a higher sensitivity of both DA receptors in HP chicks compared to LP chicks. Also stereotyped pecking is affected by Apomorphine treatment in domestic fowl (Nistico’ and Stephenson, 1979) and pigeons (Cheng and Long, 1974; Goodman, 1981). Density of DA receptors could play a role in FP. D1 and D2 receptor density has been found higher in the mST and NAc of high frequency pecking birds compared to low frequency pecking birds (Sedlackova et al., unpublished results).

7. Conclusion

With this review we highlighted the routes by which the serotonergic system is involved in and influenced by feather pecking (FP) in laying hen chickens. Feather pecking, a redirected foraging behavior, can develop as a maladaptive behavior where the animal attempts to cope with a thwarted stressful environment, but FP can also develop as a malfunctioning behavior. Genetic associations have been found between FP or feather damage and genes encoding 5-HT and DA receptors, MAO-A and immune regulatory factors. The activity of the serotonergic system appears deficient in young birds with a high FP tendency, as indicated by reduced 5-HT metabolism and turnover homogeneously in several brain areas important for executive control of foraging behavior, and in regulating emotional responses. A deficient serotonergic system in executive control pathway regions seems predisposing for FP. Serotonin activity in FP birds shows strongly influenced by 1) dysregulation of the 5-HT1A and 5-HT1B receptors reducing 5-HT synthesis and 5-HT tone, and influencing DA release, and 2) deficient MAO-A functioning decreasing 5-HT metabolism. The dopaminergic system also plays a role in pecking behavior, either directly via DA receptors, or as influenced by 5-HT receptors. Partly similar to 5-HT, young birds with a high FP tendency also show low DA activity in some specific brain areas regulating motivation to perform rewarding behavior. When FP is apparent, 5-HT and DA activity is increased in brain areas of the neurobiological network facilitating the planning and execution of goal-directed (somatic) motor behavior. Inconsistencies between studies in differences in levels of central 5-HT and DA activity between lines have been highlighted in this review. These inconsistencies in results are likely due to inclusion of FP phenotypes (feather peckers, victims, neutrals etc.) when comparing genotypes. It is important to include FP phenotypes in the analysis, as they show to differ in peripheral 5-HT and central 5-HT and central DA. Peripheral 5-HT is involved in gut health, and interestingly, birds with a high pecking tendency had low peripheral 5-HT, different gut microbiota composition and immune competence as compared to birds with low pecking tendency. Peripheral 5-HT, gut microbiota, and the immune system likely interact with central 5-HT and DA activity and could thereby influence FP and feather eating.

8. Future perspectives for research

Based on this review some aspects of the serotonergic system in relation to FP remain unknown. The 5-HT1A and 5-HT1B receptors appear important in FP, but it is unknown whether the number, sensitivity and/or density of these receptors (and other 5-HT and DA receptors) are affected in FP birds. Pharmacological treatments can further inform on intra- or extracellular mechanisms, such as SERT involvement in FP. Also, what happens during the act of FP in relation to release of 5-HT and DA is unclear. Similarly, it is unknown which changes occur in peripheral 5-HT and gut microbiota before and after the development of FP and feather eating. The role of peripheral 5-HT on gut functioning, immune system and gut microbiota seem influential when birds feather peck and when feather eating takes place. How these systems interact with the serotonergic system, and if these factors are predisposing in FP remains to be further studied.

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