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Ontogeny and Regulation of the Serotonin Transporter: Providing Insights into Human Disorders

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Abstract

Serotonin (5-hydroxytryptamine, 5-HT) was one of the first neurotransmitters for which a role in development was identified. Pharmacological and gene knockout studies have revealed a critical role for 5-HT in numerous processes, including cell division, neuronal migration, differentiation and synaptogenesis. An excess in brain 5-HT appears to be mechanistically linked to abnormal brain development, which in turn is associated with neurological disorders. Ambient levels of 5-HT are controlled by a vast orchestra of proteins, including a multiplicity of pre- and post-synaptic 5-HT receptors, heteroreceptors, enzymes and transporters. The 5-HT transporter (SERT, 5-HTT) is arguably the most powerful regulator of ambient extracellular 5-HT. SERT is the high-affinity uptake mechanism for 5-HT and exerts tight control over the strength and duration of serotonergic neurotransmission. Perturbation of its expression level or function has been implicated in many diseases, prominent among them are psychiatric disorders. This review synthesizes existing information on the ontogeny of SERT during embryonic and early postnatal development through adolescence, along with factors that influence its expression and function during these critical developmental windows. We integrate this knowledge to emphasize how inappropriate SERT expression or its dysregulation may be linked to the pathophysiology of psychiatric, cardiovascular and gastrointestinal diseases.

Keywords

serotonin transporter; gene variants; antidepressants; ontogeny; psychiatric disease; cardiovascular and gastrointestinal disease

1. Introduction

Serotonin (5-HT) is a neuromodulatory neurotransmitter serving a wide array of physiological and behavioral functions. It has become clear over recent decades that a particularly salient role of 5-HT is as a developmental signal, important for cueing proper wiring of neural circuits (see Gaspar et al., 2003 for review). It is not surprising then, that a growing literature is focused on understanding the consequences of inappropriate ambient levels of 5-HT during development for the adult phenotype. Indeed, abnormal levels of 5-

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HT result in aberrant morphology and wiring of the nervous system across species, ranging from *Drosophila* (Sykes and Condron, 2005; Daubert et al., 2010;), to *Aplysia* (Castellucci et al., 1970; Brunelli et al., 1976) to mammals (see Gaspar et al., 2003 for review). Ambient levels of 5-HT are controlled by a number of factors including rate of 5-HT synthesis and amount available for release, rate of release, rate of enzymatic breakdown, rate of diffusion through the extracellular milieu and active uptake. The serotonin transporter (SERT) is the high-affinity uptake mechanism for 5-HT. In the mature animal it is located perisynaptically on presynaptic 5-HT nerve terminals as well as on axons and 5-HT cell bodies in the raphe (Rudnick and Clark, 1993; Barker and Blakely, 1995; Blakely et al., 1998). SERTs are also expressed on non-neuronal cells including platelets (Rudnick, 1977; Hranilovic et al., 1996), lymphoblasts (Khan et al., 1996; Faraj et al., 1997), monocytes (Yang et al., 2007), enterochromaffin cells, endothelial cells (Gershon, 1999 & 2003; Wheatcroft et al., 2005) and placental syncytiotrophoblasts (Balkovetz et al., 1989). In brain, SERT is arguably the predominant mechanism controlling the strength and duration of serotonergic neurotransmission. As such, factors that perturb SERT expression and/or function during critical periods early in development might be expected to have detrimental consequences in later life. This forms the basis of the present review, which describes what is known about development of SERT in brain under normal conditions, what intrinsic and extrinsic factors can influence SERT expression and function and importantly, how perturbation of SERT early in life can contribute to psychiatric and physiological disease states in later life.

2. Developmental profile of SERT gene and protein expression

To begin, it is necessary to first summarize what is known about “normal” SERT development. Cortical neurogenesis in humans occurs between gestational week (GW) 6 and 16 (Sidman and Rakic, 1973) with neuronal migration leading to distinguishable cortical layers occurring between GW24 and GW26, an event coinciding with synaptogenesis (Huttenlocher and de Courten, 1993). With the advent of SERT specific antibodies (Qian et al., 1995) it became possible to map SERT development in human brain. In fetal brain, SERT antibodies revealed SERT-positive, thick, varicose fibers emerging from the raphe, and reaching the cortical analae at GW8, the subplate at GW10, arriving at the cortical plate at GW13 (Verney et al., 2002). These findings are consistent with those in non-human primates, where serotonergic axons have been detected in entorhinal cortex in early embryonic life of rhesus macques (Berger et al., 1993) and where the 5-HT terminal network has been shown to mature very rapidly during early postnatal life (Lambe et al., 2000; Verney 2003).

In addition to SERT-positive fibers arising from the raphe, a second type of SERT-positive fiber was detected that did not resemble classical catecholaminergic fibers (Verney et al., 2002). These non-monoaminergic SERT-positive fibers differ in several respects from those emerging from the raphe, including their anatomic location, the internal capsule, an unusual localization for monoaminergic fibers, and their transient expression between GW12 and GW14. These non-monoaminergic neurons send projections from the anterior and posterior ends of the interior capsule, which lies between the caudate and putamen, and project toward the cerebral and temporal cortex. That these fibers appear at GW12 and disappear by GW14 indicate that 5-HT may play a role in the trophic organization of the somatosensory cortex at this time (Verney et al., 2002).

One of the markers used to define fibers as monoaminergic in these studies was the presence of immunoreactivity for the vesicular monoamine transporter-2 (VMAT2). VMAT2 is responsible for taking up monoamines (including 5-HT, dopamine (DA), norepinephrine (NE)) from the intracellular fluid and storing them in synaptic vesicles, and so is a useful marker of monoaminergic processes (Henry et al., 1998). Importantly, VMAT2 serves to

store 5-HT into synaptic vesicles and protect it from degradation. While SERT and VMAT2 expression do not always go hand in hand in adult brain, for example, in certain neuronal populations within the cerebral cortex (Lebrand et al., 1998), the implications for this discourse during transient phases of early embryonic development remain unclear. Given the important trophic role of 5-HT during early development, and that excess 5-HT during these critical phases can have negative implications for the adult, it is possible that this transient period of SERT expression on non-VMAT2 expressing processes may be important for keeping 5-HT levels in check (for review see Gaspar et al., 2003).

In rodents *in situ* hybridization (Lebrand et al., 1996; Hansson et al., 1998, 1999), autoradiographic binding (D'Amato et al., 1987; Bennett-Clarke et al., 1997) and immunocytochemical (Lebrand et al., 1998; Zhou et al., 2000) approaches also reveal transient SERT gene and protein expression in brain during early development. Now, with the genetic tractability of mouse models, important insight into the physiological implications for these transient periods of SERT expression in the developing brain are being uncovered. For example, studies using SERT knockout (KO) mice have demonstrated a clear need for SERT in the normal development of thalamic projections (Persico et al., 2001; Salichon et al., 2001).

It is now well established that SERT is expressed much more broadly during development than in adulthood, and is expressed in non-5-HT neurons as well as neural crest derivatives. However, to further interrogate the expression pattern of SERT during development Narboux-Nême and co-workers (2008) inserted Cre recombinase into the SERT gene (SERT^{Cre}) of two reporter mouse lines; (1) the ROSA26R mouse, which drives LacZ expression in the cell's cytoplasm regardless of its lineage (Soriano, 1999; Narboux-Nême et al., 2008) and (2) the Tau^{mGFP} mouse which is specific to neurons (Hippenmeyer et al., 2005; Narboux-Nême et al., 2008). This enabled a fate map for SERT expressing cells to be created. The results, as anticipated, revealed remarkably broad SERT expression in non-5-HT cells during development (Narboux-Nême et al., 2008). SERT is particularly precocious in non-neural cells being robustly expressed in heart and liver at ED10.5 (Narboux-Nême et al., 2008). These results from SERT^{Cre} mice complement and extend earlier reports using *in situ* hybridization approaches (Lebrand et al., 1998; Hansson et al., 1998). Moreover, they reveal that brain regions, including CA1–CA2 of hippocampus, dentate gyrus, striatum, piriform cortex and amygdala, previously thought to transiently express SERT, (based on *in situ* hybridization or immunocytochemistry), (Cases et al., 1998; Hansson et al., 1998; Lebrand, et al., 1998; Zhou et al., 2000) do not appear to express the SERT gene at any time during development.

What is the fate of SERT after it first appears embryonically? Does SERT protein expression remain static or does its expression wax and wane? As just described, SERT protein measured by quantitative autoradiography, is first expressed during prenatal brain development on ED12 in mice, and by ED18 it is found in all of the same brain regions where 5-HT is localized immunohistochemically (Brüning et al., 1997). During the course of embryonic development, in brain regions such as the thalamus and somatosensory cortex, SERT density peaks and subsequently declines by PD7 (Brüning & Liangos 1997). During critical stages of brain development 5-HT levels can influence the expression or function of key mediators of 5-HT neurotransmission, including SERT. In the juvenile brain, SERT binding measured using a SERT selective radioligand in homogenates prepared from rodent frontal cortex, increases steadily from weaning until late adulthood (Moll et al., 2000). However, in other brain regions such as the dorsal raphe and parietal cortex, SERT density measured using quantitative autoradiography peaks and declines prior to PD20, possibly in response to a peak in extracellular 5-HT in those regions during brain development and maturation in rats (Galineau et al., 2004). In agreement with these findings in rats, Sidor et

al. (2010) more recently reported that mRNA for SERT in several regions of the dorsal raphe was highest at PD14, the youngest age examined in their study, and declined to relatively stable expression levels across the age range PD17-28 in adolescent mice.

Thus, SERT gene and protein expression is transient in some brain regions, peaks and wanes in other regions and follows a steady incline to adult levels in others. However, as discussed in the following sections, many factors can influence both total SERT protein expression as well as the plasma membrane distribution of SERT (section 3), which can be linked to negative consequences for mental and physical health (section 4).

3. Factors regulating SERT expression and function in early development

SERT expression and function is dictated by a large and diverse array of intrinsic and extrinsic factors. Studies in adult laboratory animals have revealed not only genetic variants that influence SERT activity (Murphy et al., 2004), but also auto- and hetero-receptors, via a number of kinases and phosphatases (e.g. Blakely et al., 1998; Daws et al., 2000; Ansah et al., 2003; Zhu et al., 2004, 2005, 2007), cytokines (e.g. Zhu et al., 2010), integrins (e.g. Carneiro et al., 2008), neurotrophic factors such as BDNF (e.g. Daws et al., 2007) as well as hormones (e.g. Slotkin et al., 1996a,b, 2006; Baganz et al., 2010). Extrinsic factors such as diet, environmental stressors and drugs can also have prominent effects on SERT expression and function. Less is known about how these factors might come into play during prenatal and postnatal development. The following sections review what we do know and the implications for regulation of ambient levels of extracellular 5-HT during early developmental periods.

3.1 Intrinsic factors (Genes)

The human SERT is coded by a single gene (SLC6A4) mapped to chromosome 17q11.2. It comprises 14 exons that span ~ 40 kB. Based on our current understanding, SERT is predicted to contain 630 amino acids with 12 transmembrane spanning domains. Since the human SERT was cloned in 1993 (Ramamoorthy et al., 1993), numerous gene variants have been identified that affect the expression and/or function of SERT. These have been reviewed in detail elsewhere (Murphy et al., 2004; Serretti et al., 2006; Murphy and Lesch, 2008) and so will be described only briefly here.

3.1.1. Serotonin transporter gene linked polymorphic region (5-HTTLPR)—The most well-described and common SERT variant is the SERT gene-linked polymorphic region (5-HTTLPR), originally described as a 44 base pair insertion/deletion in the promoter region which results in a short (S) or long (L) form, but now identified as a 43 base pair insertion/deletion (Heils et al., 1996; Nakamura et al., 2000; Kraft et al., 2005). The frequency of this polymorphism varies with ethnicity with the S allele generally being more prevalent in Asian populations (range 72–81%) than in Caucasian populations (ranges from 38–57%) (Lesch et al., 1996; Gelernter et al., 1997; Noshkova et al., 2008). As discussed later (see section 4), this variant has been the focus of a large and growing number of association studies in clinical populations. While the results have been mixed, there is a considerable body of evidence linking this variant to numerous psychiatric diseases.

The 5-HTTLPR affects the amount of SERT protein transcribed. Most studies measuring SERT protein expression in lymphoblasts and platelets show that carriers of the S allele express approximately half as many SERTs than individuals homozygous for the L allele (Lesch et al., 1996; Stoltenberg et al., 2002; for reviews see Murphy et al., 2004; Murphy and Lesch, 2008), but some studies have failed to replicate this finding (Preuss et al., 2000). Likewise, imaging studies of human brain have yielded mixed results, with some reporting that carriers of the S allele have reduced SERT relative to homozygotes for the L allele

(Heinz et al., 2000; Kalbitzer et al., 2010), and others reporting no difference in SERT expression among genotypes (Willeit et al., 2001; Shioe et al., 2003; Van Dyck et al., 2004; Parsey et al., 2006). Binding studies in post-mortem tissue have also failed to identify variation in SERT expression among 5-HTTLPR genotypes (Mann et al., 2000; Arango et al., 2003).

However, there are many caveats that make interpretation of data obtained from human studies often difficult, a subject recently reviewed by Willeit and Praschak-Rieder (2010). For example, many studies do not account for additional single nucleotide polymorphisms (SNPs) that occur in the SERT gene, including the promoter region (Nakamura et al., 2000; Wendland et al., 2008). One SNP occurs in the area of the L-allele, where an alanine is substituted by a guanine. This SNP is commonly referred to as the triallelic 5-HTTLPR variant and is denoted L_A/L_A , L_A/L_G and L_G/L_G . Studies which have taken into account this triallelic stratification have revealed greater SERT binding in homozygote L_A carriers than in S allele carriers, whereas L_G carriers share similar SERT expression levels as carriers of the S allele (Praschak-Rieder et al., 2007; Reimold et al., 2007; Kalbitzer et al., 2010). Along similar veins, others have reported that a significant fraction of L alleles in the 5-HTTLPR are in fact low-expressing due to interaction with another SNP, the rs25531 (Hu et al., 2006). Together with work from Wendland et al., (2008) who identified an additional SNP, rs25532, it is now clear that the traditional view of S and L alleles as low- and high-expressing, respectively, is over simplistic and must be considered in terms of the modulating effects of rs25521 and rs25532 (Wendland et al., 2008), as well as the triallelic SNP.

Selectivity of ligand can also be problematic. For example, [^{123} I]-2- β -carbomethoxy-3-b-(4-iodophenyl)tropane ([^{123} I]b-CIT) binds not only SERT, but also to the dopamine transporter (DAT) and has some affinity for the norepinephrine transporter (NET) as well. Studies using this ligand have failed to detect differences in SERT expression as a function of 5-HTTLPR genotype. In contrast, more selective ligands for SERT, such as [^{11} C]-3-amino-4-(2-dimethylaminomethylphenylthio)benzonitrile ([^{11} C]DASB), routinely reveal greater SERT expression in L_A homozygotes than in carriers of the S allele (for review see Willeit and Praschak-Rieder, 2010).

In addition, there are a multiplicity of endogenous and extrinsic factors which can influence SERT expression (see comment by Ordway, 2000) and which cannot be fully controlled in humans. For example, psychoactive drugs that target the SERT, such as selective serotonin reuptake inhibitors (SSRIs), as well as “recreational” drugs such as 3,4-methylenedioxymethamphetamine (MDMA, or “Ecstasy”) and cocaine can cause both acute effects on SERT plasma membrane expression, as well as long term effects on total SERT protein levels (e.g. Ramamoorthy and Blakely, 1999; for review see Luellen et al., 2010). Similarly, age (e.g. Pirker et al., 2000), seasonal variation (Buchert et al., 2006; Praschak-Rieder et al., 2008; Ruhe et al., 2009; Kalbitzer et al., 2010) and psychiatric condition (for reviews see Stockmeier, 2003; Meyer, 2007) are but a few of the many factors that can exert marked effects on SERT expression levels that could potentially serve to mask 5-HTTLPR genotype-dependent variations in SERT expression.

Layered onto these potentially confounding variables, is also the possibility that ligands used to measure SERT protein cannot adequately distinguish between SERT located in the plasma membrane and that in the cytosol. This raises the possibility that the inability to detect reduced SERT expression in carriers of the S allele is due to differences in plasma membrane expression of SERT. For example, carriers of the S allele may have 50% less SERT protein, but the majority of SERT may be located in the plasma membrane domain most of the time, with little, if any residing in the cytosolic compartment. This is certainly a

conceivable scenario, for example, as an adaptive mechanism to maintain relatively normal 5-HT homeostasis in the face of constitutively reduced SERT protein. In contrast, it is possible that homozygotes for the L allele may express only half of total SERT in the plasma membrane the majority of the time. This would enable L/L individuals more dynamic control over 5-HT uptake, with the ability to recruit additional SERT from the cytosolic compartment to the plasma membrane upon demand. On the other hand, carriers of the S allele would be severely limited because, according to this scenario, the majority of their SERT armamentarium would already be positioned in the plasma membrane. Of course, this scenario remains to be empirically tested, but still, provides another potential explanation for the inability of human imaging studies to consistently find reduced SERT expression in carriers of the S allele.

3.1.2. Other serotonin transporter variants, common and rare—In addition to the much studied 5-HTTLPR polymorphism, another relatively common SERT gene variant occurs as a variable number of tandem repeats in the second intron (VNTR-2) (Lesch et al., 1996; Ogilvie et al., 1996). VNTR-2 contains nine, ten or twelve copies of a sixteen- or seventeen-base pair repeat. VNTR-2 appears to be a transcriptional regulator of gene expression at this locus, but the functionality of VNTR-2 depends on which individual repeat elements are present as well as the tissue in which it is expressed (Fiskerstrand et al., 1999; MacKenzie and Quinn 1999; Lovejoy et al., 2003; for review see Murphy et al., 2004). Generally however, the VNTR-2 is associated with enhancer activity to increase SERT gene transcription.

Several other SNPs have been identified that serve to change the structure or function of the human SERT. A gain of function mutation was first reported by Kilic and co-workers (2003). This variant, in which isoleucine at position 425 is replaced by valine (I425V), has dramatically increased SERT function. This increased function could be attributed to both an increase in the maximal velocity (V_{max}) for 5-HT uptake as well as increased affinity (K_M) of the SERT for 5-HT – i.e. smaller K_M value. In 2005, the Blakely group performed a comprehensive functional analysis of ten nonsynonymous SNPs that occur in the human SERT gene (Prasad et al., 2005). They found four of the SNPs to be gain-of-function mutations, including I425V and G56A, whereas the P339L SNP resulted in a striking loss-of-function mutation. Five of the SNPs were completely insensitive to activators of protein kinase G (PKG) or p38 mitogen activate protein kinase (MAPK), two major signaling pathways regulating plasma membrane expression of SERT and its intrinsic activity (Ramamoorthy et al., 1998; Ramamoorthy and Blakely, 1999; Zhu et al., 2004; Samuvel et al., 2005; Zhu et al., 2005; Zhu et al., 2007). These and other variants have been reviewed by Murphy and colleagues (2008) so will not be discussed further here.

An interesting caveat based on the discovery of these gene variants is that because SERT density is often measured by SERT selective radiolabeled ligands in autoradiography and imaging of rodent and human brain, SNPs within SERT that alter its affinity for SSRIs and other synthetic ligands, without impeding the capacity of SERT to take up 5-HT could also introduce confounds for such measurements. For example, two SNP haplotypes (Glu39Gly and Arg152Lys) have been identified among C57 and 129S mouse lineages that impair 5-HT uptake capacity in C57BL/6 and C57BL/10 mice and reduce the [^{3} H]-labeled SSRI paroxetine binding in 129S-derived strains (Carneiro et al. 2009). As discussed earlier, SERT gene variants, if gone undetected, may lead to erroneous interpretation of binding studies in rodents and humans.

3.1.3. Serotonin transporter gene variants: Implications—The discovery of these SERT variants has two fundamentally important implications. First, when investigating the influence of a particular gene variant on SERT expression and function, the existence of all

variants need to be considered when interpreting data. Wendland and co-workers (2006) make this point most elegantly, and in efforts to enable more comprehensive genotyping, refined existing PCR protocols to provide a method to simultaneously genotype an individual for 5-HTTLPR, rs25531, VNTR-2 and Ile425 variants. As reviewed by Murphy and Lesch (2008), expression of SERT as a function of 5-HTTLPR genotype can be further modified by the co-existence of SNPs, some of which were described earlier. This knowledge is essential for furthering our understanding of how genetic variants are linked to behavioral and physiological abnormalities.

The second major implication, and one that is central to the theme of this review, is that because SERT appears early in development, these genetically encoded variants could have dramatic consequences for the ability of SERT to regulate ambient levels of extracellular 5-HT during critical developmental windows. Indeed, inappropriate regulation of extracellular 5-HT during critical stages of early development can have a profound negative effect on mood and behavior in adulthood (Gaspar et al., 2003). This will be reviewed in section 4.

3.2 Extrinsic factors (Environment)

As just discussed, precise quantitation of SERT expression and function in humans can be difficult. Interpretation of human data is also difficult because of the numerous variables that can influence SERT expression and function. However, we have gleaned tremendous insight into how intrinsic and extrinsic factors can influence SERT by using animal models, where these factors can be tightly controlled. What we have learned in terms of the developing animal is discussed in the following sections.

3.2.1. Nutritional Status and Birth Weight—Prenatal malnourishment impinges heavily on the serotonergic system in brain (Resnick and Morgane, 1984; Blatt et al., 1994; Mokler et al., 1999; Mokler et al., 2003). These results include diminished growth and arborization of 5-HT neurons in the dorsal raphe nucleus (DRN) (Díaz-Cintra et al., 1981; Blatt et al., 1994; Cintra et al., 1997a,b) and decreased 5-HT nerve terminals in hippocampus as indexed by reduced 5-HT_{1A} receptor expression (Blatt et al., 1994).

SERT expression is, not surprisingly, affected by nutritional status during fetal and early postnatal development. For example, prenatally protein malnourished rats, fostered to dams fed a standard protein diet (25% casein), exhibited a 15–25% reduction in [³H]citalopram binding to SERT in the dentate gyrus, CA1 and CA3 regions of hippocampus in adulthood (Blatt et al., 1994). Similarly, rats born to dams fed a standard chow diet but permitted access to only half that of free feeding rats, expressed dramatically reduced levels of SERT immunostaining in thalamo-cortical fibers at PD3 and PD7 (Medina-Aguirre et al., 2008). Interestingly, at 4 months of age, pups born to similarly undernourished dams showed increased SERT expression in hypothalamus (Pôrto et al., 2009), suggesting that prenatal malnourishment has brain region and/or age specific effects on SERT expression. In the case of rats fed iron deficient diets from weaning to adulthood, SERT expression was increased or decreased depending on brain region and gender. In males, SERT expression was decreased by 20–30% in several regions, including the nucleus accumbens, olfactory tubercle and colliculus, whereas in females there was a 15–25% increase in SERT expression in the olfactory tubercle, zona incerta, anteroventral thalamic nucleus and vestibular nucleus (Burhans et al., 2005).

SERT expression in later life also varies according to birth weight. It is well known that rat pups from the same litter exhibit a range of body sizes. Dependent on their position in the uterus, pups obtain differing levels of blood supply and hence nutrition; the smallest pups within a litter receive the lowest blood supply, and the largest pups the greatest (Himpel et al., 2006). Although these early postnatal differences in birth weight disappear in adulthood,

SERT expression remains correlated with birth weight. In adult (PD90) rats, SERT expression was 20% lower in the frontal cortex of those with lower birth weight compared to those with higher birth weight. In contrast, there was no difference in brain stem SERT expression. These findings suggest that low birth weight may be a risk for abnormal development of the serotonergic system in limbic regions of brain (Himpel et al., 2006).

While it is clear that prenatal or early postnatal under nutrition and birth weight can affect SERT expression, there are no studies to date that have directly studied how these extrinsic factors might influence SERT function. These studies will lend important insight into whether or not changes in SERT expression translate to an impaired ability to regulate ambient levels of extracellular 5-HT, or whether compensatory factors regulating extracellular 5-HT can overcome under or over expression of SERT protein during early development.

3.2.2. Stress—Nutrition, as just discussed, is a form of stressor, leading to increased activation of the hypothalamic-pituitary-adrenal (HPA) axis and release of stress hormones, such as corticosterone (cortisol in humans) (Lesage et al., 2006; Vieau et al., 2007). In addition to under nutrition a wide variety of stressors (or activators of the HPA axis) during early pre- and postnatal development exert profound effects on the 5-HT system and SERT expression, which may be linked to altered brain structure and wiring (Calabrese et al., 2009; Cottrell and Seckl, 2009; McEwen 2010).

When the HPA axis is activated, glucocorticoids are released, in humans this is mostly cortisol and in laboratory rodents, corticosterone. Dexamethasone is a synthetic glucocorticoid with a wide array of therapeutic uses, including treatment for preterm labor occurring between the 24th and 34th weeks of gestation (Gilstrap et al., 1995). While not associated with increased rates of neonatal death, it is associated with lower birth weight (Bloom et al., 2001). Studies investigating the effects of dexamethasone in prenatal rats reveal a striking effect on SERT. For example, maternal administration of dexamethasone during gestation (gestational day (GD) 17–19) in rats produces persistent increases in [³H]paroxetine binding to SERT in brainstem and cortex, even at low doses, below those used therapeutically. Similarly, rats administered dexamethasone on PD1–3 or PD7–9, also showed marked increases in [³H]paroxetine binding (Slotkin et al., 2006). In contrast, dexamethasone administered to mature animals failed to produce similar increases (Slotkin et al., 1996 a & b). Interestingly, the increase in SERT expression in rats given dexamethasone early in development occurred regardless of the effect on tissue 5-HT. At GD17–19 dexamethasone did not affect 5-HT levels in rats, but 5-HT levels were increased when given at PD1–3 and decreased when given at PD7–9 (Slotkin et al., 2006). These data support the idea that the effects of dexamethasone on SERT expression are not solely driven by altered presynaptic activity but likely reflect a loss of post-receptor-signaling capabilities or structural “miswiring”, where neural projections form inappropriate connections with postsynaptic cells (Kreider et al., 2006; Slotkin et al., 2006).

Similarly, other forms of stress, such as maternal separation (Vicentic et al., 2006), serve to influence SERT expression. The duration of maternal separation is a prominent factor in determining the direction of effect on SERT expression. For example, relative to non-handled and animal facility handled control rats, pups separated from their mother for 15 min daily from PD2–14 had 15–50% greater SERT expression in amygdaloid nuclei (Vicentic et al., 2006), but no change in other regions, including the cortex, nucleus accumbens, hypothalamus and hippocampus. In contrast, pups separated from their mother for 180 min daily from PD2–14 did not produce any effect on SERT expression relative to control rats in any brain region studied. One obvious caveat with maternal separation is whether the “stress” of maternal separation is overcome by the increased parenting that

follows (e.g. increased licking and grooming of pups) and raises the possibility that maternal separation is not an especially robust stressor (Millstein and Holmes, 2007). Non-the-less, a particularly interesting finding from these studies came from the “non-handled” group. Like the animal facility handled controls, these rat pups were never separated from their dam. However, whereas the animal facility handled pups were transferred to clean cages four times during PD2-14, the “non-handled” group was only touched once, on PD11, for a single cage change. The relative lack of human handling and perhaps stress associated with being housed in a soiled environment for a longer period, produced the most striking changes in SERT expression. SERT protein, as determined by quantitative autoradiography using [¹²⁵I]3β-(4-iodophenyl)tropan-2β-carboxylic acid methyl ester (RTI-55), was decreased by approximately 30–45% in hypothalamus, 20–25% in amygdala and 35% in CA3 region of hippocampus, compared to the animal facility handled control rats (Vicentic et al., 2006).

Together, these findings suggest that activation of the HPA axis early in neonatal and postnatal development may have lasting effects on SERT expression and serotonergic neurotransmission that might account for later life adverse neurobehavioral consequences. These effects however, appear to be “dose-dependent”. For example, Macrì and co-workers recently showed that resilience and vulnerability to cognitive dysfunction in adulthood were related to circulating levels of corticosterone experienced during neonatal development (Macrì et al., 2009). During the first 10 days of life, mice were given low (33 mg/l) or high (100 mg/l) corticosterone supplements via maternal drinking water. This resulted in significantly increased plasma corticosterone levels in dams at both day 5 and day 10 for high corticosterone and at day 10 for the low corticosterone condition, compared to control dams. In pups, plasma corticosterone levels were significantly higher than control for both low and high corticosterone conditions at PD5, but significantly higher only for the high corticosterone condition at PD10. The consequences of these manipulations for SERT expression in adulthood (5 months) were assayed by measuring SERT expression in blood serum. SERT in blood serum was measured using peptide fragments of SERT as antigens to detect serum natural autoantibody levels by a modified enzyme-linked immunosorbent assay (Macrì et al., 2009). In mice subjected to the low corticosterone condition there was a 2-fold increase in blood serum SERT natural antibody expression. In contrast, the high corticosterone condition had no significant effect on SERT natural antibody expression. These findings correlated with improved cognitive performance in adulthood in mice exposed to the low corticosterone condition, whereas those exposed to the higher corticosterone condition did not show any change in cognitive performance compared to control mice (Macrì et al., 2009). Indeed others have reported that “mild” neonatal stress may reduce adult stress and fear responses and increase cognitive abilities in adulthood (Catalini et al., 1993; Bredy et al., 2004; Coutellier et al., 2009) while others show that more robust neonatal stressors are linked to increased levels of anxiety and fear behavior (Romeo et al., 2003; Wei et al., 2010), although effects were often gender specific and likely strain dependent (for review see Millstein and Holmes, 2007; Mozhui et al., 2010). These and other ramifications of early life stress on risk for disease, and the potential role of SERT are discussed further in section 4.

3.2.3. Immune system activation—Immune challenge in early development is yet another stressor that serves to regulate SERT expression, at least at the level of mRNA. A recent study by Sidor and co-workers (2010) examined the effect of lipopolysaccharide (LPS, 0.05 mg/kg, i.p.) given to mouse pups at PD3 and PD5 on SERT mRNA in raphe nuclei. They found both regional and transient effects. At PD14 SERT mRNA was decreased relative to saline injected control pups in the dorsal part of the DRN. In contrast, SERT mRNA was increased in ventral and lateral parts of the DRN at PD17, while there was no effect on SERT mRNA in the median raphe nucleus (MRN) (Sidor et al., 2010).

More recently, maternal immune system activation in response to intrauterine infection in rabbit dams was reported to produce decreases in 5-HT immunoreactive fiber expression in the somatosensory cortex, reduced cortical SERT mRNA expression, and decreased 5-HT levels and tryptophan metabolism in 1-day old kits (Kannan et al., 2010). While the functional ramifications of these effects on SERT mRNA and protein expression remain to be elucidated, it is likely that activation of the immune system early in life could have dramatic effects on SERT function and subsequent control of ambient levels of extracellular 5-HT.

A rapidly growing body of literature documents prominent effects of immune function on SERT in cell systems and in adult animals. For example, interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) increase SERT mRNA and protein in cultured cells (Ramamoorthy et al., 1995; Mössner et al., 1998). Zhu and co-workers (2006) went on to show, using raphe neuron derived RN46A cells, that both IL-1 β and TNF- α cause rapid catalytic activation of SERT, which was p38 MAPK dependent. Given p38MAPK has an important role in sustaining SERT expression at the plasma membrane (Samuvel et al., 2005), immune factors that operate via this signaling mechanism could have marked effects on serotonergic neurotransmission. Indeed, Zhu et al., (2010) recently showed that LPS, via interleukin-1 receptor activation and p38MAPK dependent mechanisms, stimulated SERT activity *in vivo* and produced pro-depressive effects in adult mice.

3.2.4. Pharmacological Interventions—The behavioral effects of pharmacological blockade of SERT early in development, either by administration of SSRIs to pregnant dams or directly to pups early postnatally, has received much attention (Hilakivi et al., 1986; Yanelli et al., 1999; Ansorge et al., 2004; Ansorge et al., 2008; Forcelli and Heinrichs, 2008; Popa et al., 2008; and see Table 2 for review in Narboux-Nême et al., 2008). Unfortunately, and in contrast to the vast number of studies that have investigated the effects of SSRIs on SERT expression and function in adult animals (for review, see Luellen et al., 2010), relatively few studies have explored effects of SSRIs on SERT early in development. While reports from adult rodents are mixed, a common finding is that chronic SSRI treatment decreases SERT expression in mice (Hirano et al., 2005; Mirza et al., 2007) and rats (e.g. Brunello et al., 1987; Kovachich et al., 1992; Wanatabe et al., 1993; Pineyro et al., 1994; Benmansour et al., 1999, 2002; Horschitz et al., 2001; Gould et al., 2006, 2007; Rossi et al., 2008). Among the limited reports of the effect of chronic SSRI treatment early in development, the results appear to be compatible with those in adults. For example, rats given fluoxetine (10 mg/kg either via minipup or s.c.) from ED14-PD7 (Forcelli and Heinrichs, 2008) or ED13-20 (Cabrera-Vera and Battaglia, 1998) had reduced SERT expression in raphe, hypothalamus, hippocampus and amygdala in later life. Similarly, rats given citalopram (5 mg/kg/12 hr, s.c.) from PD8-21 displayed reduced SERT in cortex (Maciag et al., 2006). In another study, Bock and colleagues (2005) administered the SSRI fluoxetine (5 mg/kg per day s.c.) or the NET blocker reboxetine (10 mg/kg per day s.c.) to rat pups from PD2 to PD5 and then assessed the consequences for cortical SERT and NET expression in adulthood (PD90). Fluoxetine treatment resulted in a 10% increase in SERT expression in frontal cortex, but remarkably, reboxetine produced an even greater increase (20%) in SERT expression compared to saline injected control rats. Interestingly, reboxetine treatment PD2-5 had no consequence for NET expression (Bock et al., 2005). Thus, modulation of the NE system during brain development can have long term effects on SERT and the serotonergic system.

A major question that has been, and continues to be the focus of intense research, is whether these antidepressant-induced changes in SERT expression during embryonic and early postnatal periods have detrimental behavioral and physiological consequences in the long term? Data from human studies are mixed, but suggest an increased risk for serotonin

withdrawal syndrome (Sanz et al., 2005) or pulmonary hypertension (Chambers et al., 2006). As discussed in section 4.2, it is clear from rodent studies that developmental effects of SSRI administration during gestation or early postnatal life are linked to a wide range of behavioral and physiological dysfunctions. These studies in rodents suggest that even modest changes in SERT expression during these critical developmental periods can have profound consequences later in life.

Another common drug encountered during gestational and early neonatal development is nicotine. Its effects on various neurotransmitter systems have been widely studied (Ernst et al., 2001; Slotkin 2004, 2008; Slotkin et al., 2007a,b; Dwyer et al., 2008; Herrman et al., 2008; Pauly and Slotkin, 2008), but less is known about its direct effects on SERT. Recent work from the Slotkin group studied the effect of nicotine given to pregnant rats to simulate plasma levels equivalent to those found in human smokers (Slotkin and Seidler, 2010). They found that nicotine by itself elicited modest increases or had no effect on SERT expression in cortex, midbrain and brainstem in offspring aged PD30-150 (Slotkin and Seidler, 2010). However, nicotine augmented the effects of dexamethasone on SERT expression. Marked increases in SERT expression were found in cortex, midbrain and brainstem, and decreased SERT expression in striatum of male offspring. In contrast, SERT expression remained relatively static in female offspring. Interestingly, in male offspring, increased SERT expression in midbrain and brainstem were especially prominent at PD30 and PD60, whereas the effects on cortical and striatal SERT expression were strongest at PD100 (Slotkin and Seidler, 2010). Serotonin concentration was unchanged at PD2 but was subsequently decreased, and 5-HT turnover likewise showed no initial change but increased later in development. Together with measures of 5-HT receptor expression as indices of pre- and post-synaptic activity, the authors concluded that exposure to these drugs early in life serve to change the trajectory of synaptic development. Thus, even after a period of relatively normal development, abnormalities emerge later in development (Slotkin and Seidler, 2010 and references therein). Given that smoking during pregnancy increases the risk for preterm delivery, and that glucocorticoids are given to prevent preterm labor, this pharmacological combination, in part via its effects on SERT expression, likely exacerbates risk for abnormal neural function and behavior in later life, particularly in males.

3.2.5. Epigenetic Regulation—As discussed in section 3.1, gene variants affect SERT expression and function. Further regulation of SERT function can manifest via structural modifications of chromosomal regions, which serve to change gene activity without changing the nucleotide sequence, a phenomenon known as epigenetic regulation. In this regard, the rhesus macaque, which carries an orthologue of the human 5-HTTLPR (rh5-HTTLPR) has provided a valuable resource for researchers. Rhesus monkeys have been used to study the effects of early life stress by several groups (Barr et al., 2004a,b; Spinelli et al., 2007; Kinnally et al., 2008, 2010a,b). The most commonly used stressor is that of maternal separation. Infants are instead nursery reared. The Capitanio group showed that stressful experiences during infancy could influence peripheral blood mononuclear cell (PBMC) SERT mRNA expression (Kinnally et al., 2008, 2010a) and recently Kinnally and co-workers (2010c) used similar approaches to provide evidence for epigenetic regulation of SERT by early life stress. Cytosine-phosphate-guanosine (CpG) islands are regions of the genome rich in cytosine and guanine (CG) nucleotides and often located in or near promoter regions (Bird, 1986). Increased methylation of cytosines within CpG islands is linked with decreased gene transcription (Jones and Takai, 2001). In humans and rhesus macaques, an 800 bp CpG island is positioned about 200 bp downstream of the 5-HTTLPR and overlaps with the transcription initiation start site of the SERT gene. This CpG island can regulate SERT expression; for example, greater methylation of this CpG island is associated with reduced SERT expression in human lymphoblast cell lines (Philibert et al., 2007). Consistent with this finding, Kinnally and co-workers (2010c) showed that rhesus macaques carrying

the short allele of the rh5-HTTLPR had, on average, higher levels of CpG methylation than carriers of the long allele, and this was associated with lower PBMC SERT expression. Of note, higher SERT CpG methylation, but not SERT genotype, was associated with an increased ability of early life stress to produce behavioral stress reactivity in infants (Kinnally et al., 2010c). Results such as these point to CpG methylation as an important regulator of SERT expression and that epigenetic modulation of SERT during critical developmental windows might be linked to increased risk for psychiatric disease in later life.

3.2.6. Implications—Of course this is by no means an exhaustive list of factors that can affect SERT expression or function. There is evidence that other hormones such as estrogen (Maswood et al., 1999; Krajnak et al., 2003; Wihlbäck et al., 2004; Koldzic-Zivanovic et al., 2004; Bertrand et al., 2005; Sumner et al., 2007; Benmansour et al., 2009), testosterone (McQueen et al., 1999) and insulin (Figlewicz, 1999; France et al., 2009; Ramakrishnan et al., 2009; Abraham et al., 2010) as well as growth factors such as brain derived neurotrophic factor (BDNF) (Daws et al., 2007; Deltheil et al., 2008; Molteni et al., 2010) can all regulate SERT expression and/or activity in adult animals. However, to date reports that demonstrate direct effects of these factors on SERT expression and function in early development are lacking. As discussed in the following section, dysregulation of ambient 5-HT levels during critical developmental periods can have profound detrimental effects in adulthood manifesting as disorders ranging from psychiatric disease to cardiovascular dysfunction. Studies interrogating factors that can regulate the activity state of the primary mechanism controlling extracellular 5-HT, the SERT, during early developmental periods are clearly needed.

4. Abnormal SERT development and disease

So far we have reviewed factors that influence SERT expression and/or activity, including both intrinsic (heritable) and extrinsic (not heritable), during important stages of early development. However, how this relates to negative behavioral outcomes and disease states in later life remains an area of intense research and debate. The following section reviews existing literature as it relates to two key psychiatric disorders, depression and autism, as well as cardiovascular and gastrointestinal diseases.

4.1 SERT gene variants

As discussed in section 3.1, numerous variants of the SERT gene exist. Many of these have been linked to disease states, prominent among them psychiatric disorders. Not surprisingly there are thousands of reports in the literature describing various interactions and associations of these SERT gene variants and disease, and more than 75 reviews articles have been published so far. Here we focus on the relationship between SERT gene variants and some of the most widely studied disorders.

4.1.1. Depression, anxiety and related emotional disorders—Since the landmark study of Caspi and coworkers (2003) reporting an association between the 5-HTTLPR and stressful events early in life, this has been one of the most studied gene variants. The key finding was that carriers of the S allele, when exposed to early life stressful events, had a dramatically increased risk for suffering depression in later life (Caspi et al., 2003). Since this time there has been much controversy and debate, with some groups able to replicate this finding and others not (for reviews see Vergne and Nemeroff, 2006; Caspi et al., 2010; Kato and Serretti, 2010). Primary reasons for the inability to replicate this finding appear to relate to different subject populations and less stringent methodologies. For example, the majority of studies that failed to replicate relied on brief, self-report measures of stress. In contrast, studies that were able to replicate used objective indicators or face-to-face

interviews to determine stress exposure (Caspi et al., 2010). Caspi and co-authors (2010) provide a detailed synopsis of the current status of research in this field and highlight the need to adopt an inclusive approach to the literature on SERT and stress sensitivity, rather than an exclusive analysis of the literature that has attempted to replicate the original findings of Caspi and co-workers (2003) using methods that can only approximate those used in the original study. Using this criterion, there is overwhelming consensus from human studies that the S allele moderates the influence of stress on depression. This gene by environment interaction has been further cemented by use of animal models, including rhesus monkeys and rodents.

Rhesus monkeys have been an invaluable resource in this regard. As discussed earlier, they have an orthologue of the human 5-HTTLPR, which similarly, is associated with decreased transcriptional activity (Lesch et al., 1996; Barr et al., 2003; Soumi, 2006). The influence of early life stress in rhesus monkeys has been studied by separating infants from their mothers and rearing them with other infants. Monkeys carrying the S allele that have been separated from their mother show increased anxiety, agitation, stereotypies and exaggerated HPA axis responses (Barr et al., 2004; Spinelli et al., 2007), which persist into later life (Barr et al., 2004). The stress-linked S carrier phenotype in rhesus monkeys also parallels human findings in terms of brain morphology. These monkeys have abnormal cortico-limbic structure and function and reduced gray matter volume in amygdala, medial prefrontal cortex, orbitofrontal cortex and pulvinar (Jedema et al., 2010). More recently, elegant studies using boron-doped diamond microelectrodes to measure 5-HT uptake in lymphocytes from rhesus monkeys showed that 5-HT uptake was slower in carriers of the S allele, consistent with reduced SERT function in these animals (Singh et al., 2010).

Although there is no rodent orthologue of the 5-HTTLPR, genetic modification of the SERT gene in rodents has afforded a model in which experimental conditions can be very tightly controlled, recently reviewed by Kalueff et al., (2010). Mice or rats in which the SERT has been functionally excised, either by targeted mutation or chemical mutagenesis, exhibit increased anxiety-like behavior, impaired fear extinction and exaggerated HPA-axis response to acute stress (Holmes et al., 2003a,b; Homberg et al., 2007; Kalueff et al., 2010). SERT KO rats spend more time immobile in the forced swim test, a behavioral assay for negative emotion or depressed-like behavior (Olivier et al., 2008). This “depression-like” phenotype is less clear in SERT KO mice, and is largely contingent upon the background strain (reviewed in Kalueff et al., 2010). That said, there is evidence that SERT KO mice exposed to conditions known to activate the HPA axis (e.g. repeated swim, tail suspension) develop behavioral despair, a depression-like phenotype (Wellman et al., 2007). Taken together there is general agreement that SERT KO rodents display behaviors that parallel increased anxiety and depression. The relationship between SERT expression level and behavior is further exemplified by the finding that SERT overexpressing mice are less anxious (Jennings et al., 2006; Line et al., 2010), highlighting a reciprocal relationship between SERT expression and level of anxiety.

Taken together, findings in humans, non-human primates and rodents support the idea that constitutive variation in SERT expression is linked to anxiety and related behaviors. It will be interesting in future studies, using the tractability of mouse genetics, to determine if there are critical developmental windows during which inherent differences in SERT expression map adult behavior (e.g. using conditional SERT KO early developmentally), or whether persistent differences in SERT expression throughout life are necessary to support behavioral phenotypes.

4.1.2. Autism and related developmental disorders—Autism and other related developmental psychiatric disorders, extending from Asperger’s to pervasive developmental

disorders not otherwise specified (PDD-NOS), with a broad range of symptoms and severity, are complex disorders that are frequently marked by abnormalities in 5-HT metabolism and neurotransmission (Santangelo and Tsatsanis 2005; Lam et al., 2006). Blood hyperserotonemia is a hallmark of most autistic individuals and is likely due to high platelet 5-HT stores resulting from increased SERT-mediated 5-HT uptake. Blood hyperserotonemia is consistent with reports of reduced extracellular 5-HT availability and/or serotonergic neurotransmission in brain, again likely due to enhanced 5-HT uptake via SERT (Anderson et al., 1990; Chugani et al., 1999; McDougle et al., 2005; Croonenberghs et al., 2007; McNamara et al., 2008; Veenstra-VanderWeele et al., 2009). As indicated previously in this review, clinical and animal studies indicate that 5-HT plays many critical roles in regulating neuronal morphology (branching patterns, synapses, etc.) during brain development, and its perturbation may adversely alter behavior and future responsiveness to psychoactive drugs (Chandana et al., 2005; Whitaker-Azmitia 2005; Boylan et al., 2007; Murrin et al., 2007; Carola et al., 2010; Daubert and Condron 2010; Jones et al., 2010; Mulla, 2010). Since SERT is a major regulator of 5-HT neurotransmission and presynaptic 5-HT stores, it has been implicated in the etiology of autism spectrum disorders (ASDs).

Indeed, the SERT has been identified as a major candidate gene for autism in linkage and association studies for over a decade (Cook et al., 1997). Since nuanced details of how SERT expression and function can be dysregulated in autism in ethnically diverse populations are just beginning to be uncovered, controversy remains over the role played by common and rare SERT gene variants (e.g. Sakurai et al., 2008; Prasad et al., 2009). However, many studies report that function-impairing genetic polymorphisms of the SERT appear to be associated with higher risk of developing the disorder, as well as with rigid-compulsive traits, consistent with obsessive-compulsive disorder (Murphy et al., 2004; Devlin et al., 2005; Sutcliffe et al., 2005; DiCicco-Bloom et al., 2006; Moy et al., 2006). These SERT gene variants may underlie and/or contribute to some of the variability in autism phenotypes. For example, autistic carriers of the S allele of the SERT promoter polymorphism (5-HTTLPR) tend to exhibit more severe social interaction impairments, and are likely to exhibit poor response to SSRIs and antipsychotics (Tordjman et al., 2001; Murphy et al., 2004; Seretti et al., 2006; Brune et al. 2006; Dolzan et al., 2008; Henry et al., 2009). In support of reduced SERT expression contributing some role, cortical SERT density is lower in autistic children relative to age-matched controls, and SERT binding throughout many regions of brain is relatively low in autistic adult men in two independent tomography studies (Makkonen et al., 2008; Nakamura et al., 2010). However, in other reports, the long allele form of the 5-HTTLPR appears to be overtransmitted in autistic patients and/or is associated with increased aggression and repetitive behaviors (Devlin et al., 2005; Brune et al., 2006). This is consistent with findings that SSRI treatments improve aggression and social interaction in some autistic patients, while having no effect or negative effects in others (DeLong et al., 2002; West et al., 2009). Rare variants of the SERT gene may further confound interpretation of linkage and association studies for more common variants through epistatic interactions (Sutcliffe et al., 2005; Veenstra-VanderWeele et al., 2009). Some variants can also alter SERT affinity for ligands used in imaging studies, as described earlier in this review.

However, debate remains over the extent to which SERT-gene polymorphisms contribute to elevated risk for autism. A recent, global meta-analysis of familial studies found no overall association between either of the common 5-HTTLPR or VNTR polymorphisms and autism, although it did find overtransmission of the S form of the 5-HTTLPR in autistic families from US populations of mixed ethnic descent that was absent in European studies (Huang and Santangelo, 2008). The authors indicated that larger sample sizes are required for better resolution of such studies, and that a more varied suite of SERT polymorphisms or genes in or near the SERT gene should be investigated. A multiplexed variation scan study for rare

coding variants in the SLC6A4 gene found no association or frequency difference among autistic patients and controls (Sakurai et al., 2008). However, in a study of five rare SERT variants that were overtransmitted in autistic patients, including Gly56Ala, four of them enhanced SERT activity to varying degrees in ChO Flip-In cells (Prasad et al., 2009). The authors concluded that rare SERT variants may act in different ways, from enhancing SERT function (Carneiro et al., 2009) to differential phosphorylation, trafficking and catabolism (Ramamoorthy et al., 2007).

Other non-SERT gene interacting factors could also be involved at the cellular level. For example, association with platelet aggregation factors (Carneiro et al., 2008), or cholesterol composition in lipid microdomains or “rafts” that regulate intracellular turnover and transport of SERT (Magnani et al., 2004; Saher et al., 2005) could alter SERT surface availability and the balance of extracellular and intracellular 5-HT levels. The Gly56Ala mutant knock-in mouse has elevated platelet 5-HT levels, and in this respect it has construct validity with hyperserotonemic autism (Veenstra-VanderWeele et al., 2009). As those authors hypothesize, it may be that optimal SERT function may be confined to a narrow middle range, such that either over or underactivity may contribute to autism susceptibility to account for the wide range of behavioral phenotypes seen in autism.

Carriers of SERT polymorphisms may also be more susceptible to autism only in the presence of other genetic, metabolic and/or environmental challenges during critical stages of brain development. Other genetic variants that have been linked or associated with autism susceptibility that might co-occur with common or rare SERT gene variants include, but are not limited to, scaffolding protein genes such as *Deleted in schizophrenia 1* (Disc1) (Kilpinen et al., 2008), cell adhesion molecules (Wang et al., 2009), copy number variants for cell degradation markers (Glessner et al. 2009), the kinase pathway regulator PTEN (Varga et al., 2009), and the Fragile X *FMR* gene (Moy et al., 2009). Some of these dual polymorphisms have been replicated in inbred and/or transgenic mice and result in altered brain morphology and/or socially impaired phenotypes reminiscent of autism (Kwon et al., 2006; McFarlane et al., 2008; Moy et al., 2008; Page et al., 2009; Ayhan et al., 2010). Thus, multiple gene variants likely interact to impact brain ultrastructure and behaviors associated with autism and related disorders.

4.1.3. Hypertension and Cardiovascular Disorders—So far this review has focused only on SERT in brain as it relates to psychiatric disease. It would be remiss to exclude the fact that SERT is found in many tissues beyond the CNS, including those regulating cardiovascular and gastrointestinal (see section 4.1.4) function. In this section we discuss what role SERT plays in blood pressure and cardiovascular control. SERT is localized in many tissues important to blood pressure and cardiovascular control, including, platelets, pulmonary and systemic arteries, heart, endothelial cells, the adrenal as well as in the nucleus tractus solitarius in brain (Schroeter et al., 1997; Mortensen et al., 1999; Eddahibi et al., 2000; Lee et al., 2001; Huang and Pickel, 2002; Armando et al., 2003; Ni et al., 2004). Moreover, SERT appears in these areas early in embryonic development. For example, using Cre recombinase β -galactosidase staining in transgenic SERT conditional reporter mice, SERT-expressing cardiac filamentous cells in the outflow tract, arterial trunk, major heart valves and right ventricle were observed as early as ED10-18 (Pavone et al., 2008). Physiological function of SERT in these tissues is currently best understood in the pulmonary vasculature where uptake of 5-HT via SERT is necessary for 5-HT to function as a mitogen. SERT also appears to be important for vessel contractility and normal platelet function (for review see Ni and Watts, 2006). There is a rapidly growing literature showing that polymorphisms of the SERT or certain pharmacological manipulations of the SERT can have adverse implications that are associated with hypertension, thrombosis and heart disorders (Ni and Watts, 2006).

Among the most widely publicized examples is that of heart valve disease that occurred in adults treated for long periods (several months to years) with the successful weight-loss drug “fenphen” (fenfluramine plus phentermine). “Fenfen” was found to produce heart valve disease via a 5-HT-induced fibrotic reaction, in which collagen fiber overgrowth, coats and thickens the heart valves leading to cardiac malfunction from valve leakage and regurgitation (Connolly et al., 1997; Gardin et al., 2000; Jick 2000; Soler-Soler and Galve, 2000). The related drug, dexfenfluramine, as well as MDMA have also been associated with heart valve dysfunction by the same mechanism (Bhattacharyya et al., 2009). This 5-HT induced fibrotic overgrowth of heart valves has been replicated in rodent studies. For example, when 20 mg/kg 5-HT was administered to adult rats daily for 3 months, similar collagen-rich carcinoid plaques developed (Gustafsson et al., 2005). A common feature of these drugs is that they are all substrates for SERT and increase circulating 5-HT levels by causing the release of 5-HT via SERT. Given that such severe heart valve dysfunction can develop within a few months in adults in response to SERT mediated elevations in systemic 5-HT levels, it is not surprising that SERT dysfunction or blockade can produce cardiac abnormalities during embryonic and postnatal development and growth (Yavarone et al., 1993; Sari and Zhou, 2003).

Related to this, a subject of some debate is whether administration of SSRI antidepressants to women during pregnancy and early postpartum can contribute to cardiac dysfunction in offspring. As discussed previously, SSRIs work by increasing extracellular 5-HT by inhibiting its uptake via SERT. Some clinical studies indicate administration of SSRIs such as citalopram, fluoxetine, sertraline, or paroxetine during pregnancy may double the risk of minor cardiac defects in offspring (Diav-Citrin et al., 2008; Pedersen et al., 2009). Others suggest that risks of neonatal cardiac malformations from SSRI exposure during pregnancy are negligible and/or transient (Costa et al., 2004; O’Brien et al., 2008; Klinger and Merlob, 2009). Recent rodent studies, where experimental conditions can be tightly controlled, show that prenatal and neonatal SSRI exposure can have lifelong detrimental effects on cardiac function (Fornaro et al., 2007; Noorlander et al., 2008). While no firm conclusion can be drawn regarding prenatal SSRI exposure in humans and persistent cardiovascular disease, it appears from rodent studies that maternal SSRI use may pose a significant risk, warranting further studies in this area.

While early pharmacological blockade of SERT may adversely affect cardiac function in later life, polymorphisms of SERT also contribute certain risk. For example, among carriers of polymorphisms impairing SERT function, there is an increased risk for heart disease (Serretti et al., 2006; Otte et al., 2007). Indeed, histological investigation of the heart valves of SERT KO mice revealed collagen fibrosis of both heart valves and myocardial tissue that was significantly greater than that in wildtype mice. In addition, the left ventricles of KO mice were dilated and functioned less efficiently (Mekontso-Dessap et al., 2006). In SERT KO rats, systolic blood pressure does not differ from wildtype rats at baseline, however in SERT+/- rats blood pressure is slightly elevated at baseline and remains so under hypertensive conditions (Homberg et al., 2006 as in Monassier et al., 2010). Such findings in rodents imply that function-impairing SERT gene polymorphisms should be considered a major risk factor for cardiac dysfunction.

On the other hand, pulmonary hypertension has been linked to SERT overexpression. For example, hypertension resulting from overgrowth of smooth muscle cells in the pulmonary artery is reportedly more common in carriers homozygous for the L allele of the 5-HTTLPR polymorphism. (Eddahibi et al., 2001). A subsequent study by the same research group confirmed that primary pulmonary hypertension was associated with overexpression of the SERT in pulmonary artery smooth muscle and lung cells (Marcos et al., 2004). Consistent with these findings, in SERT knock-in (overexpressing) mice, pulmonary hypertension is

also observed (MacLean et al., 2004). Likewise, SERT density is higher in spontaneously hypertensive rats compared to control Wistar Kyoto rats (Roessner et al., 2009). In other rodent studies, pulmonary hypertension induced by monocrotaline (MCT) challenge to rats also increases SERT expression. Interestingly, atorvastatin (Lipitor), which is used clinically to reduce risk for heart attack or stroke, is effective in reversing both outcomes (pulmonary hypertension and SERT overexpression) of MCT treatment in rats (Laudi et al., 2007). Similarly, MCT-induced pulmonary artery hypertension in rats was reversed by 12 weeks of fluoxetine administration, however it returned after fluoxetine withdrawal (Zhu et al. 2009).

In sum, it appears that deficiencies in SERT expression or function leading to an excess in circulating 5-HT may lead to fibrotic overgrowths producing heart valve malformations, while overexpression of SERT in pulmonary smooth muscle can lead to pulmonary hypertension. Taken together with potentially unhealthy diet and behavior often exhibited by patients with depression and related psychiatric disorders, which are also associated with polymorphisms of the SERT, the effects of SERT dysfunction (above or below an ideal “normal level”) can compound the risk of cardiovascular disease (Otte et al., 2007; Williams et al. 2008). With the rising prevalence of childhood hypertension, related in part to the rapidly growing incidence of childhood obesity (Feber and Ahmed, 2010), the consequences for abnormal development of serotonergic (and other systems) as a result warrant deeper investigation. These data suggest that hypertension in children might also contribute to 5-HT and SERT linked pathologies in later life.

4.1.4. Gastrointestinal disorders—The gut contains 95% of all 5-HT in the body and extracellular levels are regulated by SERT, which is found on all mucosal epithelia cells (Gershon, 1999). Enterochromaffin cells in the gut release copious amounts of 5-HT, which serves to help regulate gastrointestinal (GI) fluid secretion and gut motility (Ormsbee and Fondacaro, 1985; Gershon, 1999). It is no surprise then that dysfunction of SERT in the gut could have adverse effects.

The relationship between irritable bowel syndrome (IBS) and SERT polymorphisms has been among the most studied. While the results have been mixed, three case controlled studies indicate a positive association between the 5-HTTLPR SS genotype and the diarrhea-predominant subgroup of IBS sufferers, whereas others find no association (Van Kerhoven et al., 2007; Colucci et al., 2008). Still others find associations between carriers of the LL genotype and improved treatment response to the 5-HT₃ receptor antagonist, alosetron (Camilleri, 2004). Certainly the importance of considering the complexities of IBS, including not only multiple genetic factors, but also multiple environmental variables, must be considered and likely factor into these conflicting reports (see Colucci et al., 2008). Of interest however, is the finding that SERT KO mice have increased GI motility and diarrhea with occasional constipation reminiscent of an IBS-like clinical syndrome (Chen et al., 2001).

There are few studies addressing IBS or other GI abnormalities as a consequence of early developmental perturbations to SERT. Of those, a recent study reported higher intestinal 5-HT levels and lower SERT mRNA in pediatric patients presenting with IBS (Faure et al., 2010). In addition, there is evidence to suggest that inflammation of the gut, via inflammatory mediators including interferon- γ and tumor necrosis factor α , reduces SERT expression and function (Mawe et al., 2006; Linden et al., 2003 & 2005; Wheatcroft et al., 2005; Foley et al., 2007). Together, these reports raise the possibility that early life infections, particularly of the gut, might lead to chronic GI diseases later in life.

4.1.5. Other disorders—Studies of SERT KO mice and rats have been informative, not only about the disorders discussed so far in this review, but have also afforded insight into

the role of SERT in many others (Murphy et al., 2008; Kalueff et al., 2010). For example, SERT KO and heterozygote mice have disrupted sleep patterns (Wisor et al., 2003) and increased susceptibility to pentylenetetrazole-induced seizures (Fox et al., 2007). Sensory function is reduced in SERT KO mice (Vogel et al., 2003; Ren-Patterson et al., 2005), and in female SERT KOs bladder responses to stretching are reduced (Cornelissen et al., 2005). SERT KO mice also appear to have reduced muscle strength (Holmes et al., 2002) and reduced bone weight, thickness and structural resistance to fracture, where the most marked changes occur in weight-bearing bones (Bliziotes et al., 2002; Warden et al., 2005; Sample et al., 2008). Related to obesity, diabetes and other metabolic disorders these mice also exhibit decreased glucose tolerance and insulin sensitivity and increased body weight, particularly with age (reviewed in Murphy et al., 2008). Unfortunately, while extracellular and tissue levels of 5-HT in adult SERT heterozygote and KO mice have been well documented (Bengel et al., 1998; Mathews et al., 2004; Shen et al., 2004; Kim et al., 2005; Fox et al., 2008), we know little about how 5-HT levels are changed early in development of rodents or primates with impaired SERT function. It may be that extracellular levels of 5-HT do not mirror those of adults, but may be exacerbated (or not), contingent upon the developmental profiles of other transporters capable of 5-HT uptake and which might compensate (or not) for impaired SERT function (see Daws, 2009). Clearly there is much to be learned about the factors controlling extracellular 5-HT during embryonic and early postnatal development. Importantly, understanding how overcoming abnormal levels of 5-HT at these early developmental stages will be critical for curbing, or preventing, long term behavioral and physiological consequences.

4.2 Behavior and disease linked to pharmacological blockade of SERT during childhood or adolescent periods

4.2.1 Prenatal and early postnatal SSRI exposure effects—A recent review of safety and efficacy of SSRI administration to pregnant women and adolescents indicates potential adverse effects (Olivier et al., 2010). Acute SSRI withdrawal symptoms such as agitation are reported in infants, however delayed psychomotor development, altered pain response, cardiovascular abnormalities and increased risk of depressive disorders later in life are potential long term side effects of pre or postnatal SSRI exposure (Casper et al., 2003; Andersen and Nalvalta, 2004; Oberlander et al., 2005; De las Cuevas and Sanz 2006; Tuccori et al., 2009; Alwan and Friedman, 2009; Gentile, 2010).

Similar adverse physiological, neuroanatomical and behavioral effects have been observed in rodent models of early-juvenile and prenatal SSRI or tricyclic antidepressant exposure. In these rodent models dendritic spine formation and neuronal branching are permanently reduced; anxiety is increased, shock avoidance is decreased, cocaine-seeking behavior is increased, and other impairments of 5-HT function occur, some of which persist into adulthood (Andersen and Nalvalta, 2004; Borue et al., 2007; Forcelli and Heinrichs, 2008). In rats, prenatal (GD13-20) exposure to the SSRI fluoxetine (10 mg/kg sc daily injection of dam) decreased 5-HT content in the frontal cortex by 28% in juvenile (PD26) but not in adult (PD70) males. Only in midbrain did low 5-HT levels persist through to adulthood (Cabrera-Vera et al., 1997). Exposure to fluoxetine from PD0-6 resulted in reduced dendritic spine growth and fewer dendritic projections which altered tactile and thermal responsivity and locomotor activity in adolescence (Lee et al., 2009). In guinea pig offspring from dams administered fluoxetine (10 mg/kg/d) by osmotic minipump throughout their pregnancy, there were no adverse effects on weight gain and no higher incidence of still births, but pain threshold was lower in offspring exposed in utero to fluoxetine (Vartazarmian et al., 2005). In swiss and C57BL/6 mice administered fluoxetine from 2 to 6 weeks of age (for the first week by subcutaneous osmotic minipump and then via fluoxetine in the drinking water) there was an apparent anxiogenic effect of fluoxetine in a battery of behavioral tests that were

conducted beginning at 5.5 weeks of age (Oh, et al., 2009). Other effects of early juvenile SSRI exposures, prior to PD21 in rodents, which affect behavior persistently into adulthood include altered 5-HT receptor densities, abnormal cortical neuron structure, increased anxiety and stress responses, decreased aggression and altered REM sleep patterns, as reviewed in Narboux-Nême et al. (2008 see Table 2 within) and in Homberg et al., (2010). Of particular interest, the SSRI, fluoxetine, but not the NE reuptake inhibitor, desipramine, given to mice from PD4-21, exposure affected emotional behavior in adulthood, producing reduced adult exploration in the elevated plus maze and open field tests and increased the latency to feed or escape shock in new environments (Ansorge et al., 2008). The timing of such exposures in rodents corresponds with late gestational development in humans (Rice and Barone, 2000; Brent, 2004) suggesting that fetal exposure to SSRIs may produce long lasting effects on emotional behavior (Oberlander et al., 2009).

4.2.2. Effects of SSRIs during juvenile and adolescent brain development—

In contrast to prenatal or early-life exposures to SSRIs under conditions of maternal treatment, treatment of children or adolescents with SSRIs can be better titrated; however, the long-term implications of SERT blockade during these developmental periods is not well understood and potential behavioral and long term effects of SSRIs on developing brains remain a major concern (Andersen and Navalta, 2004; Murrin et al., 2007; Alwan and Friedman, 2009; Homberg et al., 2010; Mulla 2010).

In 2003 the British Department of Health and in 2004 the Food and Drug Administration (FDA) mandated warning labels for all SSRIs indicating use in children may increase risk of suicide, due to reports of suicidal attempts or thoughts among children treated with SSRIs in the 1990s (Vitiello and Swedo, 2004; Olfson et al., 2006). A more recent comparative assessment of SSRIs and tricyclic antidepressants administered to children and adolescents indicated that all of these drugs increased risk of suicide to a similar extent (Schneeweiss et al., 2010). After the warning, SSRI treatment in children declined, yet suicide rates remained the same, and no alternative drug has filled the void left by SSRIs for children with psychiatric disorders (Katz et al., 2008). A new clinical trial of the S-enantiomer citalopram, which is the second SSRI (following fluoxetine) approved by the FDA for treatment of depression in children, indicated that it did not differ from placebo in the number of suicides attempted (Yang and Scott, 2010). Together, these results suggest that suicidality may not be related to SSRI treatment per se, but a risk associated with the disease itself. None-the-less, given the prevalence of polymorphisms in SERT and variance in metabolism of SSRIs, exploring alternative 5-HT uptake mechanisms (described in section 5), may be a useful direction for future investigations in efforts to identify new targets for the treatment of these disorders in children and adolescents.

Child and adolescent neurotransmitter systems may not respond to SSRIs as adult systems do, in part because some mature sooner than others (serotonergic vs. noradrenergic), and expression and function of receptors and transporters differs during the course of juvenile development (Bylund and Reed, 2007; Liberzon and George, 2010; Murrin et al., 2007; Mulla 2010). Baseline extracellular neurotransmitter levels above an ideal normative range may produce hyperactive behavior, but further drug-induced increases may have the opposite effect, assuming a U-shaped dose-effect curve, which is why psychostimulants such as the amphetamines administered to children with attention deficit hyperactivity disorder (ADHD) can effectively reduce hyperactivity (Andersen, 2005).

Studies examining mid to late juvenile and adolescent exposures to SSRIs in rats and mice have yielded mixed results. For example, while adolescent fluoxetine exposure has been reported to have no lasting adverse effects on anxiety or stress response in adulthood in C57BL/6 and BALB/c mice (Norcross et al., 2008), other studies report age and strain

dependent differences in response to the acute effects of SSRIs. For example, fluoxetine failed to produce antidepressant-like effects in the forced swim and tail suspension tests in juveniles of any strain (BALB/c, C57, and a C57/129S hybrid strain), but was effective in adult mice of C57 and C57/129S strains, but not in BALB/c mice (Mason et al., 2009). One mechanism by which SSRIs may exert their beneficial therapeutic effects is through neurogenesis, but again, rodent studies have revealed that this neurogenic effect is age and strain dependent. For example, in BALB/c and C57BL/6 mice, adult hippocampal neurogenesis only occurred when treatment commenced in adolescence (PD35), and this effect was abolished by stress (Navailles et al., 2008). A gender by age comparison of peri-pubescent and adult rats, showed that fluoxetine did not enhance hippocampal neurogenesis in either male or female adolescents to the same extent as it did in adults (Hodges et al., 2009). In sum, it appears that long term effects of SSRI treatments in juvenile rodents exert subtle effects on the adolescent brain, and further studies are needed to assess whether some SSRIs may have better risk/benefit profiles than others for the developing brain. Studies such as these, geared toward identifying developmental (age) and genetic (strain and genes) factors that influence response to antidepressant drugs will be important for optimizing treatments for specific age groups and genetic background.

4.2.3. Implications—Rodent studies of SSRI treatment early in development clearly show that the effects on behavior and physiology only occur when SSRIs are given in these early periods. These effects are not recapitulated when SSRIs are given later in development (Ansorge et al., 2004 & 2008; see also Table 2 in Narboux-Nême et al. 2008 and review by Oberlander et al., 2009). Likewise, as discussed earlier in this review, there is a strong interaction between stressful life events early in life and increased probability of suffering from depression, anxiety and related disorders, which do not occur when stress occurs later in life (Caspi et al., 2010; Oberlander et al., 2009). Preclinical studies in rodents and clinical studies in humans reveal striking parallels in the behavioral and physiological ramifications following these extrinsic early life perturbations of SERT (see Oberlander et al., 2009). Together with the fact that intrinsic factors, such as genetic reduction in SERT function, also increases risk for psychiatric and other disorders in later life, it is clear that SERT exerts a major influence on the developing brain, (as well as other organs and tissues). In this regard, finding ways to “normalize” extracellular levels of 5-HT in these critical early developmental periods is an important area for continued research. One such avenue of research is to explore alternative mechanisms for 5-HT uptake.

5. Alternative transporters for serotonin: Role in disease and treatment response

So far we have discussed SERT in relative isolation, as the only mechanism for 5-HT uptake in brain. However, while SERT may be the transporter with the highest affinity for 5-HT, there is a rapidly growing body of literature reporting the presence of non-SERT 5-HT transporters that can play a significant role in mediating 5-HT neurotransmission (reviewed in Daws, 2009). These include the well-known NET and DAT, but also the organic cation transporter (OCT), particularly the OCT3 subtype, and plasma membrane monoamine transporter (PMAT), for which a role in biogenic amine neurotransmission has only recently been realized. It stands to reason, therefore, that these transporters might act to compensate for reduced SERT expression or function, particularly early in development. While there is evidence from rodent studies showing that, in adult mice, DAT (Pan et al., 2001; Zhou et al., 2002) and OCT3 (Baganz et al., 2008) can compensate, at least in part, for 5-HT uptake, nothing is known about the role of non-SERT 5-HT transporters in regulating ambient 5-HT during development. Likewise, how such ectopic uptake of 5-HT might predispose to disorders early in life or later in adulthood, as well as influence subsequent treatment

response, remains unclear. Using antidepressant response as an example, the following section summarizes what little we do know and ends by proposing a hypothesis through which this might occur.

5.1 Ontogenic profiles of biogenic amine transporters and antidepressant response: What do we know?

Remarkably little is the answer, and even more so when one narrows the developmental window to “adolescent”. As discussed in section 4.1. there is now considerable evidence that the S allele of the 5-HTTLPR is linked to several disorders, primary among them depression and related psychiatric disorders, and often these individuals do not respond well to currently available antidepressant medications (Rausch, 2005; Serretti et al., 2007). However, age is an even stronger predictor of antidepressant response. Children and adolescents respond poorly compared with adults (Bylund and Reed, 2007). The SSRI, fluoxetine (Prozac) is currently the only available treatment for depression approved by the FDA for children and adolescents up to 18 years old and escitalopram (Lexapro) is approved for adolescents age 12 and older. The lack of therapeutic options for this age group is compounded further by a recent report that treatment response to the SSRI, citalopram, in children and young adults carrying the S allele, was especially poor (Kronenberg et al., 2007). Given the high prevalence of adolescent depression, affecting 4–8% of the population with an incidence of 25% by the end of adolescence (Kessler et al., 2001) and, of major concern, the particularly high prevalence of suicide in this young population, (the third leading cause of death in the 15 to 19 year age group) (Reed et al., 2008), it is clear there is an urgent need to understand the neural mechanisms accounting for these differences between adolescents and adults, with the hope to uncover more effective treatments.

Again, rodent studies are lending a hand. In rodents, PD21 is considered juvenile and PD28, early adolescent (Bylund and Reed, 2007; Hefner and Holmes, 2007; Pechnick et al., 2008; Reed et al., 2008). Consistent with clinical responses in humans, SSRIs are effective in reducing the time spent immobile in the forced swim test (FST), an index of antidepressant-like activity, in rats as young as PD21 as well as in adults, whereas NET blockers, such as the tricyclic, desipramine (DMI), are ineffective in the FST in rats younger than PD28 (Pechnick et al., 2008; Reed et al., 2008). The mechanistic basis for these findings remains to be determined, but is generally thought attributable to delayed maturation of the NE neurotransmitter system relative to 5-HT. In terms of the actual drug targets themselves, SERT and NET, ontogenic profiles for their expression during this developmental window are sparse. Galineau and co-workers (2004) reported a triphasic profile for SERT. In terminal regions such as amygdala and hypothalamus, expression peaked around PD21, decreased at PD28 and plateaued through PD70, the oldest age tested. For NET, Sanders and co-workers (2005) reported that NET expression in the CA3 region of hippocampus was 3-fold less in rats aged PD20 compared to PD25 and adults. Thus, based on studies in rats, expression of SERT and NET appears to positively correlate with the emergence of an antidepressant-like response to SSRIs and NET blockers. The ontogeny of DAT more closely resembles that of NET, with expression increasing steadily until plateauing at adult levels at P28 (Galineau et al., 2004).

What about OCT3? To our knowledge there are no published reports of its ontogeny in brain or even in peripheral organs. For its closely related subtype, OCT1, mRNA expression reaches adult levels by P15 in kidney and by P22 in liver (Alnouti et al., 2006). Although difficult to translate these findings to those which may occur in brain, these data support the idea that in juveniles, OCT3 may reach adult levels earlier than SERT and NET. Of note, in adults, OCT3 is widely expressed in SERT rich brain regions, anatomically positioning OCT3 to take up 5-HT (Gasser et al., 2009).

What about PMAT? Likewise, there are no published reports of its ontogeny in brain, or in periphery, perhaps not surprising since it was identified and cloned relatively recently, in the mid-2000s (Engel et al., 2004; Engel and Wang, 2005). Like OCT3, in adult mice PMAT is a widely distributed, neuronally-expressed transporter, which is co-expressed in many regions containing SERT, supporting a role for PMAT in 5-HT uptake, at least under certain conditions (Dahlin et al., 2007).

Taken together the possibility is raised that non-SERT mediated 5-HT uptake during childhood and adolescence may account for poor treatment response to SSRIs by buffering the increase in extracellular 5-HT that is believed to be the first step to initiating the cascade of events that ultimately lead to therapeutic response (see Daws 2009). This could be further compounded by developmental windows where there is disproportionately high expression (and/or function) of non-SERT transporters for 5-HT compared to SERT. While this remains to be determined empirically, it provides one plausible mechanism for the relative lack of therapeutic benefit of SSRIs in children and adolescents.

5.2. The corticosterone-sensitive organic cation transporter 3: Linking early life stress and 5-HTTLPR behavioral phenotypes

Corticosterone is a potent antagonist of OCT3, but not other biogenic amine transporters including SERT and PMAT (Engel et al., 2004; Gasser et al., 2006; Koepsell et al., 2007) and is ~100-fold more selective for OCT3 than OCT1 or OCT2 (Hayer-Zillgen et al., 2002). This suggests that corticosterone, released in response to stress, may tamper with 5-HT neurotransmission during development by blocking 5-HT uptake via OCT3. Indeed evidence that OCT3 function is modulated by stress in adult animals comes from reports that in dorsomedial hypothalamus, a site where stress and glucocorticoids acutely modulate 5-HT neurotransmission, stress or injections of corticosterone rapidly increase extracellular 5-HT (Feng et al., 2005). Of note, the increase in 5-HT following corticosterone was greater than an equivalent dose of an SSRI (Feng et al., 2005; see also Feng et al., 2009, 2010). Elegant *in vitro* studies by Gasser and co-workers (2006) showed that this increase in 5-HT was likely mediated by OCT3. Consistent with the increase in extracellular 5-HT following corticosterone, reduction of OCT3 function using either antisense or pharmacological approaches reveal an antidepressant-like response in rodents (Kitaichi et al., 2005; Baganz et al., 2008 & 2010).

We recently found that expression and function of OCT3 is significantly increased in SERT heterozygote mice, which have reduced SERT expression, and provide a model for human carriers of the S allele (Baganz et al., 2008). Moreover, blockade of OCT3 elicited antidepressant-like effects in SERT mutant mice but not wildtype mice (Baganz et al., 2008). Since OCT3 can take up 5-HT with high capacity and the stress hormone, corticosterone, is a potent blocker of OCT3, the intriguing possibility that OCT3 might be an important mechanism contributing to dysfunction of serotonergic neurotransmission during early life stress, is raised. It is well known that abnormally high levels of extracellular 5-HT during critical periods in brain development can modify wiring of brain circuitry and cause long lasting changes in adult behavior (Gaspar et al., 2003). Extracellular 5-HT is already increased 5-fold in SERT^{+/-} mice and 9-fold in mice lacking the SERT compared to wildtype mice (SERT^{+/+}) (Shen et al., 2004; Mathews et al., 2004). Corticosterone released in response to early life stress, by blocking OCT3, may lead to even greater levels of extracellular 5-HT in brain of SERT^{+/-} and SERT KO mice and exacerbate the deleterious behavioral phenotypes that can emerge in adulthood. Indeed, such a possibility may help to explain why early life stress increases the probability of suffering depressive illness in later life in carriers of the S allele of the 5-HTTLPR (Caspi et al., 2003 & 2010; Serreti et al., 2006). Put another way, low SERT activity (S carriers) may create risk in the face of stress because there is not enough SERT function to compensate for the loss of OCT3 function that

results from its blockade by corticosterone released in response to stress during development. This will be an exciting line for future research that may allow us to glean new insight into the underlying etiology of this gene $\times$ stress interaction and identify new targets for preventative or therapeutic intervention.

6. Concluding remarks

It is clear from the literature that there are an overwhelming number of intrinsic and extrinsic factors that can influence SERT expression and/or activity from early embryonic periods through adolescence. While these factors continue to affect SERT expression and function throughout adulthood, it seems that such modulation of SERT during early periods in development are especially important for ensuring “normal” development. Given the complex interplay between neurotransmitter systems, this extends beyond “normal” development of the serotonergic system, but also to the myriad of neurotransmitter systems that are affected by 5-HT, which combined, orchestrate appropriate wiring of brain circuitry. Figure 1 provides a summary cartoon of what has been covered in this review of the literature, which highlights some of the vast array of factors that can influence SERT expression and/or activity. In the case of early developmental windows, embryonic through adolescence, the majority of studies have focused on the influence of these factors on SERT expression. At this time, essentially nothing is known in terms of how these factors influence SERT activity, for example, by catalytic activation or trafficking to and from the plasma membrane, during these critical developmental windows. We do know that extracellular levels of 5-HT peak and wane during early development. However, we are yet to establish how increases or decreases in SERT expression and/or activity may be mechanistically linked to mistiming of these peaks and troughs in extracellular 5-HT during development. What has emerged from the literature is a clear link between aberrant SERT expression and a host of disorders ranging from psychiatric (e.g. depression, ASD) to physiological (e.g. cardiovascular, gastrointestinal). There is much yet to be understood about the mechanics of this relationship, which is and will continue to be the subject of intense research for many years to come. Ultimately, the hope is that such lines of research will help to elucidate the etiological bases for these disorders and subsequently the design of improved therapeutics or preventative interventions.

Abbreviations

CpG	Cytosine-phosphate-guanosine
DA	dopamine
DAT	dopamine transporter
DRN	dorsal raphe nucleus
ED	embryonic day
GD	gestational day
GW	gestational week
HPA	hypothalamic-pituitary-adrenal
IBS	irritable bowel syndrome
KO	knockout
MAPK	mitogen activate protein kinase
MDMA	3,4-methylenedioxymethamphetamine

MCT	monocrotaline
NE	norepinephrine
NET	norepinephrine transporter
OCT	organic cation transporter
PMAT	plasma monoamine transporter
PD	postnatal day
SSRI	selective serotonin reuptake inhibitor
SNP	single nucleotide polymorphisms
VNTR-2	variable number of tandem repeats in the second intron
VMAT2	vesicular monoamine transporter-2
5-HT	serotonin, 5-hydroxytryptamine
SERT/5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter linked polymorphic region
+/+	wildtype
+/-	heterozygote
-/-	null; knockout

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Figure 1.

A complex web of factors can affect SERT expression and/or activity during embryonic and early postnatal development. SERT is the primary, high-affinity uptake mechanism for 5-HT and plays a major role in regulating levels of extracellular 5-HT. While 5-HT levels normally peak and wane during development, mistiming, or inappropriate magnitudes of these peaks may contribute to a host of 5-HT-linked pathologies in later life. Abnormal SERT function at critical times during development might contribute to the manifestation of inappropriate 5-HT levels.