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Drugs of abuse and human placenta

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Abstract

Drugs of abuse such as cocaine and amphetamines, when used by pregnant women, exert deleterious effects on the fetus. These drugs produce their effects through inhibition of the serotonin transporter, norepinephrine transporter, and dopamine transporter. The inhibition can occur in the pregnant mother as well as in the fetus. These events contribute to the detrimental effects of these drugs on the fetus. However, the role of placenta, which serves as the link between the pregnant mother and the fetus, in the process remains understudied. It has been assumed that placenta did not play any direct role in the process except that it allowed the passage of these drugs from maternal circulation into fetal circulation. This was before the discovery that placenta expresses two of the three monoamine transporters. The serotonin transporter and the norepinephrine transporter are expressed on the maternal-facing side of the syncytiotrophoblast, thus exposed to the inhibitory actions of cocaine and amphetamines if present in maternal blood. Inhibition of these transporters in placenta could lead to elevation of serotonin and norepinephrine in the intervillous space that may cause uterine contraction and vasoconstriction, resulting in premature delivery, decreased placental blood flow, and intrauterine growth retardation. Thus, the placenta is actually a direct target for these abusable drugs. Since the placental serotonin transporter and norepinephrine transporter are also inhibited by many antidepressants, therapeutic use of these drugs in pregnant women may have similar detrimental effects on placental function and fetal growth and development.

Keywords

Placenta; Monoamine transporters; Serotonin transporter; Norepinephrine transporter; Cocaine; Amphetamines; Pregnancy

Introduction

Placenta is a unique organ in a number of ways. The functional cell of the placenta, namely the trophoblast, plays multiple roles to promote the growth and development of the fetus (Gude et al., 2004). It is the sole link between the pregnant mother and the fetus. It plays an obligatory role in the transport of nutrients from mother to fetus, thus functioning like the small intestine in the adult (Smith et al., 1992; Jansson et al., 2009; Desforges and Sibley, 2010). It also plays an essential role in the elimination of metabolic waste products from the fetus. The metabolic waste products are transported from fetal circulation into maternal

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Conflict of interest

The author declares that there are no conflicts of interest.

circulation via the placenta so that the metabolites can be removed ultimately via maternal liver and kidneys. Thus, the placenta functions like the liver and kidneys in the adult. Placenta also performs functions similar to the lung in the adult by mediating gas exchange to deliver oxygen to the fetus and to eliminate carbon dioxide/bicarbonate from the fetus. In addition, it is also an important endocrine organ, producing large quantities of steroid hormones (progesterone and estrogen) that are essential for the maintenance of pregnancy. Detailed studies have been carried out to understand the broad range of physiologic functions of this pluripotent organ at physiological and biochemical levels, but relatively little is known on the potential role of this organ in mediating the pharmacological effects of therapeutic drugs and drugs of abuse on the fetus. Since the normal function of the placenta is an absolute necessity for optimal growth and development of the fetus, interference in the functions of the placenta by pharmacologic agents will compromise fetal growth and development. It is well recognized that the drugs of abuse such as cocaine and amphetamines, when used by women during pregnancy, have significant detrimental effects not only on the mothers but also on their fetuses (Plessinger and Woods, 1998; Plessinger, 1998; Kaltenbach, 2000; Addis et al., 2001). But, the role of placenta in mediating these detrimental effects has not received much attention. The present review focuses on the evidence available in the literature to support the idea that placenta is not simply an inactive bystander in the unwanted side effects of abusable drugs on the developing fetus. The evidence clearly points to the contrary. The placenta serves as a direct target for these drugs, which compromises the normal essential functions of this organ, thus resulting in significant negative effects on the developing fetus.

Structure of the placenta

There are certain unique features in the structure of the placenta and blood circulation in this organ that are directly relevant to pharmacologic actions of cocaine and amphetamines (Osolo and Mandala, 2009). The placenta is of fetal origin and its blood circulation on the maternal side is established by destruction of blood vessels in the uterine tissue at the site of placental invasion of decidua. As a result, uterine arterioles bring the blood to the placental tissue and uterine venules drain the blood from the tissue. The placental villi are thus bathed directly in maternal blood without the intervening endothelial cells. The functional unit of the placenta is the trophoblast cell. There are two types of this cell: cytotrophoblast is undifferentiated, which when differentiated, fuse to each other to form the syncytiotrophoblast. Because of the fusion, the syncytiotrophoblast is multi-nucleated and its plasma membrane consists of only two parts, one in contact with maternal blood and the other facing the fetal side (Ganapathy et al., 2000). There are no lateral membranes. The maternal-facing membrane is highly convoluted so as to increase the surface area for optimal transfer of nutrients from mother to fetus. Hence, this membrane is called “brush border” membrane or apical membrane. The fetal-facing membrane is called basal membrane. These two membranes are distinct with the expression of different sets of enzymes and transporters in each. Thus, the placental syncytiotrophoblast is a polarized cell, capable of vectorial transfer of nutrients from mother to fetus and at the same time capable of vectorial elimination of metabolic waste products from fetus to mother. Adjacent to the basal membrane lie the fetal blood vessels that circulate the blood between the developing fetus and the placenta through the umbilical cord. In term placenta, the cytotrophoblast layer is almost nonexistent. Thus, the fetal blood circulation is separated from the maternal blood circulation in the placenta only by a single cell layer, namely the syncytiotrophoblast. This is the basis for the characterization of the human placenta as “hemomonochorial.”

Effects of cocaine and amphetamines on pregnant women – past ideas

Even though it was well recognized in the past that abuse of cocaine and amphetamines during pregnancy led to significant deleterious effects on the pregnant mother as well as on the developing fetus, no one believed that placenta played any active role in this process. The effects of these drugs on the mother were thought to be primarily due to the blockade of the norepinephrine uptake system in sympathetic neurons and in the uterine muscle (Volpe, 1992). Inhibition of neuronal norepinephrine uptake system leads to increased sympathetic activity, resulting in cardiac stimulation and vasoconstriction with consequent hypertension. This causes a significant decrease in blood flow in the uterine tissue, leading to decreased perfusion of the placenta. As a result, transfer of essential nutrients as well as oxygen from mother to fetus is compromised. At the same time, blockade of uterine muscle norepinephrine uptake increases extracellular norepinephrine, which enhances uterine contraction. These effects on placental perfusion and uterine contraction were believed to be responsible for intrauterine growth retardation and premature delivery, which are often observed in women who abuse cocaine and amphetamines during pregnancy (Volpe, 1992; Plessinger and Woods, 1998; Plessinger, 1998; Kaltenbach, 2000; Addis et al., 2001). In addition, these drugs were thought to cross the placenta, most probably via diffusion. Once inside the developing fetus, the drugs block the uptake of norepinephrine in sympathetic neurons in the fetus, leading to cardiac stimulation and vasoconstriction, actions similar to those seen in the mother. This causes hypertension in fetus, consequently affecting its growth and development.

Effects of cocaine and amphetamines on pregnant women – present ideas

None of the past ideas regarding the possible mechanisms of action of cocaine and amphetamines in pregnant women is incorrect, except the notion that placenta played only a passive role in the process. It has become clear in the past two decades that placenta is a direct target for these drugs (Ganapathy and Leibach, 1994, 1995). Placenta expresses norepinephrine transporter, the same transporter responsible for the uptake of norepinephrine in sympathetic nervous system (Ramamoorthy et al., 1992, 1993a; Jayanthi et al., 1993). In addition, placenta also expresses serotonin transporter, which is also a target for cocaine and amphetamines (Balkovetz et al., 1989; Ramamoorthy et al., 1995a). These two transporters are located in the placental syncytiotrophoblast, principally expressed in the maternal-facing brush border membrane, thus in direct contact with maternal blood. Therefore, when women use these drugs during pregnancy, the drugs block the functions of the norepinephrine transporter and the serotonin transporter in the placenta, thus making the placenta a direct target for cocaine and amphetamines (Ganapathy and Leibach, 1994, 1995; Nguyen et al., 1999).

It is important to understand the physiological functions of the norepinephrine transporter and the serotonin transporter in the placenta to recognize the pharmacological consequences of the blockade of their functions by cocaine and amphetamines in terms of fetal growth and development. Placental blood flow on the maternal side is very unique due to the absence of capillary network. The syncytiotrophoblast is bathed in maternal blood with no endothelial cells in between. We speculate that this situation is very similar to hemorrhage. Uterine arterioles bring the blood to the placenta and uterine venules drain the blood from the placenta. The placental villi come in direct contact with blood. An advantage of the absence of the endothelial barrier is that the transfer of nutrients and oxygen from mother to fetus is more efficient due to the lack of an extra cell layer between the maternal blood and the syncytiotrophoblast. The disadvantage is that the hemorrhage-like situation may increase the risk for platelet activation and consequently clotting. However, it is very obvious that clotting does not occur in placenta in normal pregnancy. There are indeed mechanisms in

place in placenta that effectively prevent platelet activation and clotting (Lanir et al., 2003). In spite of these preventive mechanisms, we speculate that platelets may still be activated to some extent in the intervillous space within the placenta. Activation of platelets is expected to release serotonin (De Clerck, 1990; Vanhoutte, 1991). Since serotonin is a potent vasoconstrictor as well as a stimulator of uterine contraction, serotonin must be removed from the intervillous space effectively so as to prevent the actions of serotonin on uterine blood vessels and uterine muscle. The serotonin transporter expressed in the brush border membrane of the syncytiotrophoblast is likely to participate in this process (Fig. 1). The placental serotonin transporter is identical to the transporter that is responsible for the clearance of serotonin from the synaptic cleft of serotonergic neurons (Ramamoorthy et al., 1993b). This is a very active transporter, energized by three different driving forces, namely a Na^+ gradient, a Cl^- gradient, and a K^+ gradient (Balkovetz et al., 1989; Ramamoorthy et al., 1993b). The energetic features of this transport system are ideally suited to clear the vasoactive serotonin from the intervillous space within the placenta very effectively. It is interesting that there is an apparent similarity between the physiological functions of the serotonin transporter in the serotonergic nervous system and the placenta. In the serotonergic nervous system, the presynaptic neurons, when activated, release serotonin into the synapse to relay signals to the post-synaptic neurons. Once the signal is relayed from the presynaptic neuron to the post-synaptic neuron, the actions of serotonin must be terminated. This is where the serotonin transporter comes to play a role. The serotonin transporter is expressed in the plasma membrane of the presynaptic neurons, and the function of this transporter is to clear serotonin from the synapse so that the neurotransmission is terminated (Fig. 2). The intervillous space between the mother and the placenta functions similar to the synapse. Platelets in the maternal blood within the placenta are activated to some extent because of the lack of endothelium, releasing serotonin in the intervillous space, but this serotonin will have deleterious effects on placental perfusion if not cleared. The actions of serotonin are however prevented because of the effective role of the placental serotonin transporter in the removal of serotonin (Fig. 1). Once inside the syncytiotrophoblast, serotonin is metabolized by monoamine oxidase, an enzyme present abundantly in the placenta (Carrasco et al., 2000; Sivasubramaniam et al., 2002). Thus, the syncytiotrophoblast functions like a sink for serotonin. If this function is blocked by cocaine and amphetamines, serotonin will accumulate in the intervillous space, leading to uterine contraction and vasoconstriction. As a result, premature delivery, decreased placental blood flow, and intrauterine growth retardation might ensue.

The actions of norepinephrine on uterine muscle and blood vessels are similar to that of serotonin. In addition, norepinephrine induces platelet activation. Therefore, an effective mechanism in the placenta to reduce the levels of norepinephrine in the intervillous space would be beneficial for optimal placental function. This is what the norepinephrine transporter expressed in the brush border membrane of the syncytiotrophoblast does (Fig. 1). This function is again similar to the role of norepinephrine transporter in noradrenergic neurons where the transporter is responsible for the clearance of norepinephrine from the synaptic cleft (Fig. 2). It is important to note that the placental norepinephrine transporter is identical to the norepinephrine transporter expressed in the nervous system, both coded by the same gene (Ganapathy and Leibach, 1994, 1995; Nguyen et al., 1999).

Cocaine and amphetamines exhibit potent inhibitory effects on the serotonin and norepinephrine transporters expressed in the placenta. The inhibition constants for cocaine, amphetamine, and methamphetamine to block the transport function of the placental serotonin transporter are 0.15, 9.0, and 13.6 μM , respectively (Prasad et al., 1994; Ramamoorthy et al., 1995a). The corresponding values for the blockade of the placental norepinephrine transporter are 0.55, 0.09, and 0.22 μM (Ramamoorthy et al., 1993a; Ramamoorthy et al., 1995a). Therefore, the serotonin transporter is blocked more potently

by cocaine than by amphetamines whereas the norepinephrine transporter is blocked by amphetamines more potently than by cocaine. These inhibition constants are of pharmacological significance because cocaine and amphetamines are found at these relevant concentrations in blood of individuals who abuse these drugs. As a result, one can expect that the functions of the serotonin transporter and the norepinephrine transporter in the placenta would be affected significantly in women who use cocaine and amphetamines during pregnancy. Cocaine blocks the functions of the serotonin and norepinephrine transporters, thus compromising the ability of these transporters to clear serotonin and norepinephrine from the intervillous space (Fig. 3). Amphetamines, on the other hand, compete with serotonin and norepinephrine for transport via the two transporters, thus competitively inhibiting the clearance of serotonin and norepinephrine from the intervillous space (Fig. 3). Even though the modes of interaction of cocaine and amphetamines with the serotonin and norepinephrine transporters are different, the end result is the same; that is, the removal of serotonin and norepinephrine via the transporters is inhibited by these drugs, thus resulting in the elevation of these vasoconstrictive and uterotonic monoamines in the intervillous space.

Human placenta also expresses two other targets for cocaine. These are the extraneuronal monoamine transporter, also known as organic cation transporter 3 or OCT3 (Kekuda et al., 1998; Wu et al., 1998), and the sigma receptor 1 (σ R1) (Ramamoorthy et al., 1995b; Kekuda et al., 1996). OCT3 is expressed in the fetal-facing basal membrane of the syncytiotrophoblast (Sata et al., 2005). The physiological function of this transporter and its relevance to placental biology are not known at present. Moreover, even though the transport function of OCT3 is inhibited by cocaine, relatively high concentrations are needed to cause significant inhibition of the transporter (Amphoux et al., 2006). Therefore, it is not clear whether or not this transporter plays any role in the pharmacological actions of cocaine in the placenta. σ R1 is not a transporter but plays an important role in cellular signaling (Hayashi and Su, 2007; Tsai et al., 2009). It is located primarily in intracellular membrane compartments, particularly in the endoplasmic reticulum. It is important to note that progesterone serves as an endogenous ligand for this receptor (Seth et al., 1998; Ganapathy et al., 1999). Cocaine interacts with the receptor at pharmacologically relevant concentrations (Chen et al., 2007). Therefore, it is likely that the function of the receptor in the placenta is compromised to a significant extent in women as a result of cocaine abuse during pregnancy.

Relevance of the serotonin transporter and the norepinephrine transporter in the placenta to the transplacental transfer of cocaine and amphetamines

Cocaine is lipophilic, and therefore can cross the lipid-rich biological membranes passively without participation of any specific transporter. Cocaine interacts with the active sites of the serotonin transporter and norepinephrine transporter and thus prevents the transport of serotonin and norepinephrine via the respective transporters. Several studies have demonstrated high-affinity binding of cocaine analogs to serotonin transporter (Meyer et al., 1996; Amara and Sonders, 1998). Therefore, even though the serotonin transporter and the norepinephrine transporter are inhibited by cocaine competitively, cocaine is not a transportable substrate for these transporters (Fig. 3). The drug functions as a blocker of the transporters. Nevertheless, the presence of cocaine in the maternal blood blocks the entry of serotonin and norepinephrine into placental syncytiotrophoblast and consequently prevents the clearance of these vasoactive monoamines from the intervillous space. In contrast, amphetamines serve as competitive substrates for the two transporters (Meyer et al., 1996; Amara and Sonders, 1998). Amphetamine and methamphetamine compete with serotonin and norepinephrine for binding to the active site of the respective transporters and prevent their transport into syncytiotrophoblast. Instead of the monoamine substrates, amphetamines

enter the placental cell via the transporters (Fig. 3). Thus, the placental serotonin and norepinephrine transporters mediate active entry of amphetamines into placenta. We speculate that OCT3 present in the fetal-facing basal membrane of the syncytiotrophoblast may facilitate the transfer of amphetamines from the placenta into fetal circulation.

Use of antidepressants during pregnancy and its consequences in terms of placental function

A wide variety of antidepressants elicit their pharmacological effects in humans by blocking the functions of the serotonin transporter and the norepinephrine transporter. Such drugs include the selective serotonin reuptake inhibitors (SSRIs) such as Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), and Celexa (citalopram), and the serotonin and norepinephrine reuptake inhibitors (SNRIs) such as Effexor (venlafaxine) (Iversen, 2000; Gutman and Owens, 2006). Tricyclic antidepressants such as Norpramin (desipramine) and Tofranil (imipramine) also block the functions of the serotonin transporter and the norepinephrine transporter (Iversen, 2000; Gutman and Owens, 2006). Many of these antidepressants are used increasingly in pregnant women for treatment of depression. The pharmacological consequences of such use in terms of placental function and fetal growth and development need careful evaluation. Since the actions of these antidepressants on the placental serotonin transporter and the norepinephrine transporter are the same as those of cocaine and amphetamines, one can speculate that the consequences in terms of placental function and fetal growth and development must also be the same. There have been several studies suggesting intrauterine growth retardation and premature delivery as a result of antidepressant use during pregnancy (Kallen, 2007; Way, 2007; Wisner et al., 2009). In view of the present recognition that human placenta is a direct target for these antidepressants, controlled studies are needed to evaluate carefully the consequences of antidepressant use during pregnancy.

Potential connection between drug-induced blockade of the functions of the placental serotonin transporter and norepinephrine transporter and mother-to-fetus transmission of HIV

The intactness of the placental structure as a barrier is an essential requirement for the prevention of transfer of HIV (human immunodeficiency virus) from mother to fetus during pregnancy. Adequate blood flow and oxygenation are obligatory for the structural integrity of the placenta and hence for the maintenance of its barrier function. Inhibition of the serotonin and norepinephrine transporters in the placenta by cocaine and amphetamines has potential to compromise this barrier function due to decreased blood flow resulting from increased levels of serotonin and norepinephrine in the intervillous space. This has serious clinical implications because of the well-known connection between drug abuse and increased risk for HIV infection.

Conclusions

The discovery of abundant expression of serotonin transporter and norepinephrine transporter in human placenta has expanded our understanding of the actions of cocaine and amphetamines in pregnant women. These findings have shown unequivocally that placenta is not simply a bystander in the pharmacological actions of these abusable drugs on pregnant women as once thought, but actually plays an active role in the process. Placenta serves an obligatory function in the growth and development of the fetus. The expression of various molecular targets for cocaine and amphetamines in this important organ indicates that the biological functions of the placenta are most likely compromised by the presence of these

abusable drugs in the mother during pregnancy. Since serotonin and norepinephrine are highly active as vasoconstrictive and uterotonic agents, inhibition of the functions of the serotonin transporter and norepinephrine transporter in the placenta by cocaine and amphetamines could increase the levels of these monoamines in the intervillous space, leading to vasoconstriction and uterine contraction and consequently compromising placental function and also causing premature delivery. This new knowledge adds to our current understanding of the molecular mechanisms involved in the deleterious effects of cocaine and amphetamines on the growth and development of the fetus.

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Fig. 1. Physiologic functions of the serotonin transporter (■) and norepinephrine transporter (●) in human placental trophoblast. 5HT, serotonin (also called 5-hydroxytryptamine); NE, norepinephrine; E, epinephrine. These two transporters are located on the maternal-facing brush border membrane of the trophoblast.

Fig. 2.
Roles of the serotonin transporter and norepinephrine transporter in the nervous system. A, serotonin transporter; B, norepinephrine transporter; V, vesicular monoamine transporter; 5HT, serotonin; NE, norepinephrine; Trp, tryptophan; MAO, monoamine oxidase; Phe, phenylalanine; Tyr, tyrosine; DA, dopamine.

Fig. 3. Differential actions of cocaine and amphetamines on placental serotonin and norepinephrine transporters. 5HT, serotonin; NE, norepinephrine; ■, serotonin transporter; ●, norepinephrine transporter.