

Introduction

Cocaine binds to and blocks the activity of monoamine transporters which results in a decreased monoamine re-uptake at the synapse and increased extracellular levels of these neurotransmitters. Cocaine can act both in CNS and in PNS, stimulating CNS and increasing sympathetic tone. It can cross the placenta barrier by simple diffusion so its mechanisms of action can exert significant teratogenic effects on the developing foetus. In addition, it can also act as an intrauterine stressor. Dopaminergic system develops early during gestational period so it can be affected by prenatal cocaine exposure (PCE). Specific areas of the human brain such as frontal lobe and limbic system are thought to be particularly vulnerable to the prenatal exposure to cocaine.

Aims

- Study the neurobiological and behavioural effects of prenatal cocaine exposure on children and adolescents.
- Clarify if there are significant differences in brain development, physical growth and behaviour between exposed and non-exposed subjects.

Methodology

Literature research on online databases, mainly PubMed and ScienceDirect. Consult basic textbooks of neurophysiology and neurobiology of addiction.

Brain abnormalities

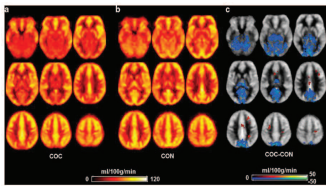


Fig. 1. Quantitative resting CBF image for the cocaine and control groups. (A) Mean CBF image for the cocaine group. (B) Mean CBF image for the control group. (C) Quantitative differences between the two groups (cocaine-control; blue -> CBF is higher for controls, and red -> CBF is higher for cocaine exposed subjects). CBF decrease in the occipital and thalamus regions for the cocaine group vs. the control group (Roussotte et al., 2010).

- Whole-brain volumetric study in **children** reported reduced cortical gray matter volume (GMV) and total parenchymal volumes in children prenatally exposed to cocaine (results lost statistical significance if exposure to other drugs was considered). Others reported significant reduced GMV in occipital and parietal lobes and white matter reductions in the corpus callosum, which were related to altered neurocognitive performance. A fMRI study reported 10% decrease in global cerebral blood flow in adolescents with prenatal cocaine exposure (PCE).

- In **non-human primates** early brain growth is compromised -> significant alterations in cortical cytoarchitecture including inappropriate positioning of many cortical neurons, loss of normal lamination, and reductions in the cortical volume, density and total number of cortical neurons.

- Studies with **mouse** -> total smaller cortical thickness, particularly in the supragranular compartment (layers I-IV) in animals exposed to high doses.

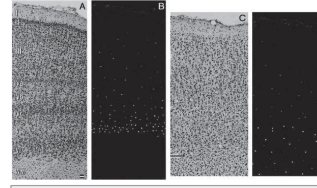


Fig. 2. Micrographs of the cortex of the calcarine sulcus (primary visual cortex) of 3-year-old rhesus monkey. (A) Coronal sections from a not exposed animal. This cortex has clear laminar structure. (B) Dark field image of the same sections. Heavily radiolabeled cells occupy a narrow band corresponding to cortical layer V. (C) Coronal sections from an exposed animal. This cortex has a homogenous appearance with an increased number of cells in the white matter. (D) Dark field image of the latter section. The heavily labeled cells are dispersed in the white matter as well as in the deep cortical layers; WM=white matter. Scale bar=400µm (Lidow et al., 2003).

Effects on physical growth

- **At birth (children):**
 - ✓ Preterm birth
 - ✓ Generalized growth retardation (reduced birth weight, length and head circumference)
- **At 10 years of age (children):**
 - ✓ Reduction in weight, length, head circumference, body mass index, probability to be obese.
 - * Specific data from Gale et al., 2013:
 - Weight -> 4.54 kg less (41.73 vs. 46.27kg, $p < .01$)
 - Length -> 2.54 cm shorter (144.78 vs. 147.32 cm, $p < .04$)
 - Head circumference -> 6 mm smaller (540 vs. 546 mm, $p < .05$)
 - BMI -> reduction of 19.4 vs. 21.4, $p < .05$
 - Obesity -> less likely to be obese (12 vs. 33% > 95th percentile, $p < .001$)
- Other factors have to be considered -> environment, life-style, infections, nutrition, genetics, and psychosocial status.

Behaviour regulation difficulties

- **Executive functioning:** PCE -> less optimal executive functioning including working memory, inhibitory control, problem solving, attention, planning and others. Important to study it in children and adolescents because it can have implications for the decision making abilities.

- ✓ **Attention and inhibitory control:** PCE may increase the risk of attention and inhibitory control problems, especially in males. Go/no-go reversal task study results showed that PCE had significant effects on attention errors in males and a trend of highly exposed males to show more inhibition errors. Similar results in a Stroop task study. The effects were dose related.

- ✓ **Externalizing problems** are those behaviours related outwards/towards other people, e.g. delinquency and aggressiveness. PCE is considered a risk factor for externalizing problems but there are many other risk factors such as exposure to other drugs of abuse and foster or adoptive care than can have an influence on it. PCE was correlated with aggressiveness in males (children and young rats) and male gender was considered a predictor for increased externalizing problems.

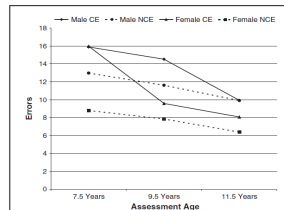


Fig. 3. Trajectory of errors during the Stroop colour-word task performance by gender and prenatal cocaine exposure status (Bridgett et al., 2013).

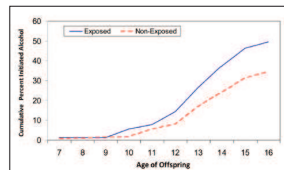


Fig. 4. Age of alcohol initiation among offspring exposed and not exposed to cocaine first trimester (Richardson et al., 2013).

- **Substance use** is considered a risk-taking behaviour and has been associated with PCE and also with high-risk social and cultural environments.

- ✓ Adolescents exposed to cocaine during the 1st trimester of gestation showed high risk of substance use and early substance use initiation (mainly alcohol, marijuana and tobacco, but also cocaine).

- ✓ Lower GMV in frontal and posterior parietal cortex of PCE adolescents increased the probability of having initiated substance use and substance use.

- ✓ Higher quality home and caregiver settings do not reduce rates of substance use among prenatally exposed adolescents.

- ✓ Other predictors would be violence exposure, pubertal maturation and male gender.

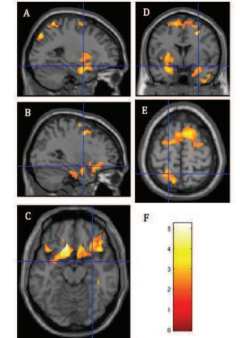


Fig. 5. Regions of significantly lower gray matter volume in prenatally-exposed than noncocaine-exposed adolescents. (A) Left insula and amygdala. (B) Right amygdala and inferior frontal gyrus. (C) Ventral frontal cortical regions: orbitofrontal cortex and inferior frontal gyrus. (D) Superior frontal gyrus, left and right amygdalae, and left insula. (E) Posterior parietal cortex and superior frontal cortex. (F) Colour bar representing the height of the voxelwise t statistics in panels A-E. See crosshairs at Rando et al., 2013.

Cognitive abilities

- PCE alone does not lower general intelligence (IQ).
- PCE is associated with high need of individualized education plan and specialized support services.
- PCE has a direct negative impact on language skills, improvement with age.
- Higher quality home and caregiver settings can have some protective effects.
- Influence of other factors.

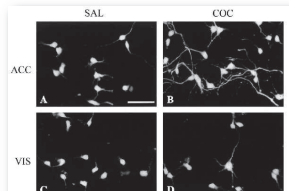


Fig. 6. Photomicrographs of MAP-2-stained embryonic day E21 medial frontal cortical (including ACC) (A, B) and Visual cortex (VIS) (C, D) culture preparations. Neurons taken from the AAC of (COC)-exposed embryos (B) demonstrate an exuberant growth of neurites as compared to those from (SAL)-exposed embryos (A). There were no differences between neurons taken from the VIS of SAL (C) and COC (D)-exposed embryos (Harvey et al., 2004).

- It has been described that PCE in rabbit produces a specific uncoupling of the D₁ dopamine receptor from its G_s protein in the caudate nucleus, frontal cortex and cingulate cortex (strongly innervated by dopaminergic fibers), possibly due to an adaptative reaction to the persistent increase in synaptic dopamine during development.

- Stimulation of D₁ dopamine receptor -> suppression of axonal neurite outgrowth.

- Increased dopamine -> uncoupling of D₁ dopamine receptor -> decreased suppression -> increased length and decreased bundling of layer III and V of pyramidal neuron dendrites and alterations in GABA and parvalbumin expression interneurons.

- Structural abnormalities in the frontocingulate cortex may be associated with deficits in attentional and associative processes.

Uncoupling of D₁ dopamine receptor

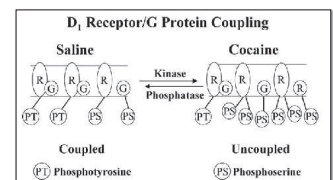


Fig. 7. The equilibrium between coupled and uncoupled (desensitized) states of the D₁ receptor is determined by the rate of phosphorylation of serine by a protein kinase and the rate of dephosphorylation by phosphatase 1. Prenatal cocaine exposure produces a dysregulation that results in a permanent decrease in protein phosphatase 1. Consequently, the equilibrium shifts to an increase in the phosphorylated state of the receptor (Harvey et al., 2004).

Conclusions

- PCE can have an influence on certain aspects of brain development, physical growth and behavioural regulation. However, there are many other risk factors that can have an impact on them and the results are not always consistent.
- Some of the possible limitations of the studies may be that in human experiments it is difficult to control for other variables such as the exact timing and dose of cocaine, use of other drugs, socioeconomic status and others, that most of the human studies are done in the United States and that the number of individuals studied may, in some cases, not be large enough to obtain statistically significant results. In animal studies some of these limitations can be solved although it is risky to generalize the results of animals and consider them valid to humans.

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