Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in nonhuman primates

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The views expressed herein are those of the presenter and do not necessarily reflect those of the Food and Drug Administration

Goal: Make predictions about the effects of developmental exposures to anesthetic agents on cognitive function in humans.

Ideally, the data needed to make such predictions are obtained from laboratory animal models in well controlled experiments under known conditions of exposure

* The use of appropriate animal models is critical: the closer to humans, the better.

* Relevant endpoints decrease the uncertainty associated with the process; utilization of identical endpoints is best.

Ketamine anesthesia and abnormal brain cell death

- Sensitive period in the monkey includes ~middle of third trimester (GD 120) to postnatal days 5/6; no effect in PND 35 offspring
- 24 hours initially used as a benchmark. 3 hours does not appear to be sufficient; 9 hours is sufficient...subsequently 5 hours also shown to be effective
- Cell death is both apoptotic and necrotic in the monkey; in rat it is apoptotic

Is early postnatal ketamine anesthesia associated with subsequent cognitive deficits in rhesus monkeys?

- Given that ketamine causes significant abnormal cell death during the brain growth spurt/synaptogenesis in the primate as it does in rodents, are there associated functional consequences as there are in rodents?

Early postnatal ketamine anesthesia and long lasting cognitive deficits in rhesus monkeys

- 24-hr iv ketamine anesthesia on PND 5 or 6
- Wean at 6 months of age
- Begin OTB behavioral assessments at 7 months of age: daily 50 min sessions (M-F)
- Monitor for at least two years (currently at ~750 sessions, ~150 weeks/38 months (>3 years) of testing; animals now ~4 years old)

National Center for Toxicological Research (NCTR) Operant Test Battery (OTB) Assessments

- Motivation
- Color and Position Discrimination
- Learning
- Short-term Memory
FOR THE COLOR AND POSITION DISCRIMINATION TASK
- All three press plates are used
- Initially, either a red, yellow, blue or green color is presented at the center position
- Observation of this color is indicated by a subject's response to it (color is extinguished)
- Side plates are immediately illuminated when
- If center had been either red or yellow, left is correct, if blue or green, right is correct

FOR THE SHORT-TERM MEMORY AND ATTENTION TASK
- All three press plates are used
- Initially, one of several symbols is presented as a 'sample' at the center position
- Observation of the sample symbol is indicated by a subject's response to it (sample is extinguished)
- After one of several time delays (e.g., 1-32 seconds), three choice symbols are presented (one 'matching' the sample)
- Responding to the 'match' is correct

FOR THE LEARNING TASK
- All four retractable levers are used
- Serial position and correct and incorrect indicator lights are used
- Subjects must learn a different sequence of lever presses each test session
- Sequences of 1 to 6 levers acquired in a single session
Color and Position Discrimination Task

Learning Task

Cases of comparable behavioral effects of drugs in both humans and rhesus monkeys

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary Acute Effect</th>
<th>Monkey Reference</th>
<th>Human Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>overestimate time passage</td>
<td>Schulze et al. 1988</td>
<td>Hicks et al. 1984</td>
</tr>
<tr>
<td>marijuana smoke</td>
<td>short-term memory impairment</td>
<td>Schulze et al. 1989</td>
<td>Darley et al. 1974</td>
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<tr>
<td>chlorpromazine</td>
<td>decrease response initiation</td>
<td>Ferguson et al. 1992</td>
<td>Tecce et al. 1975</td>
</tr>
<tr>
<td>diazepam</td>
<td>learning &amp; memory impairments</td>
<td>Schulze et al. 1989</td>
<td>Ghoneim et al. 1984</td>
</tr>
<tr>
<td>morphine</td>
<td>decrease response rates</td>
<td>Schulze &amp; Paule 1991</td>
<td>Goldberg et al. 1982</td>
</tr>
<tr>
<td>atropine</td>
<td>learning disruption</td>
<td>Schulze et al. 1992</td>
<td>Higgins et al. 1989</td>
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<tr>
<td>pentobarbital</td>
<td>overestimate time passage</td>
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<td>Goldstone et al. 1958</td>
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<td>marijuana smoke</td>
<td>amotivational syndrome</td>
<td>Paule et al. 1992</td>
<td>Lantner 1982</td>
</tr>
<tr>
<td>cocaine (prenatal)</td>
<td>decreased cognitive flexibility</td>
<td>Chelonis et al., 2003</td>
<td>Richardson 2006</td>
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*THC = delta-9-tetrahydrocannabinol
Summary

- Proof of concept that a single episode of ketamine-induced general anesthesia during a sensitive period of brain growth can cause subsequent cognitive deficits in nonhuman primates
- These effects are long-term: years (permanent?)
- Effects are seen in behaviors thought to reflect aspects of brain function related to IQ

Questions that remain

- What is the threshold duration of exposure to cause these functional deficits?
- Is it the same as the threshold for causing abnormal cell death?
- How long will functional deficits manifest? Follow-on assessments are under way but appears to be very long-lasting or permanent.
- What is the exact period of sensitivity to these effects? How much earlier than GD 120 and later than PND 5 or 6?
- How does this period of sensitivity relate to human development?

Reference

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Neurotoxicology and Teratology

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