Hepatotoxicity of novel psychoactive substances structurally related to MDMA and methamphetamine

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Novel psychoactive substances

• “designer drugs”, “legal highs”,
• Sellers bypass the law by misleading labeling
• 101 new NPS in 2014 in the EU
• Only scarce pharmacological & toxicological data available

Objective of the study

• *In vitro* hepatotoxicity of 6 stimulant novel psychoactive substances (NPS)
• Comparison of the NPS to the popular drugs of abuse MDMA (“ecstasy”) and methamphetamine

www.saferparty.ch
MDMA: a known hepatotoxin


[Acute liver failure caused by methylenedioxymethamphetamine ('ecstasy')].
[Article in Dutch]
de Man RA, Wilson JH, Tjen HS.


Acute liver damage and ecstasy ingestion.
Ellis AJ, Wendon JA, Portmann B, Williams R.


Ecstasy: a common cause of severe acute hepatotoxicity.
Andreu V, Mas A, Bruguera M, Salmerón JM, Moreno V, Nogué S, Rodés J.


Ecstasy induced fatal hepatic failure.
Colak Y, Tuncer I, Enc FY, Ozturk O, Kiziltas S, Ulasoglu C.
Drugs included in the study

Classic drugs of abuse:

- MDMA
- Methamphetamine

NPS:

- Mephedrone
- Methedrone
- Methylone
- MDPV
- Naphyrone
- 6-APB
Cytotoxicity and ATP content

- Luciferase-based assays
- 2 human hepatic cell lines (HepG2 & HepaRG)
Cytotoxicity and ATP content

24 h treatment of HepG2 & HepaRG cells

Adenylate kinase release (% of control)

ATP content (% of control)
Cytotoxicity and ATP content

24 h treatment of HepG2 & HepaRG cells

Adenylate kinase release (% of control)

ATP content (% of control)

- HepG2
- HepaRG
Mitochondrial membrane potential

- Measurement with positively charged fluorescent dye that enters the mitochondria
Mitochondrial membrane potential

24 h treatment of HepG2 cells

![Graphs showing mitochondrial membrane potential changes with different concentrations of MDPV and naphyrone. The graphs depict the percentage of control values (% of control) for mitochondrial membrane potential ($\psi_m$) as a function of concentration (mM). The graphs indicate significant effects at certain concentrations.]

- **MDPV Graph**: The graph shows a decrease in $\psi_m$ as the concentration of MDPV increases. There is a significant drop at 1 mM, indicated by ***.
- **Naphyrone Graph**: The graph shows a consistent decrease in $\psi_m$ with increasing concentration of naphyrone. There is a significant decrease at 1 mM, indicated by **.

Chemical structures for MDPV and naphyrone are depicted in the graphs, showing their molecular formulas.
Reactive oxygen species and glutathione levels

- $O^2-$ levels measured with fluorogenic dye
- tGSH levels measured with enzymatic recycling method
Reactive oxygen species and glutathione levels

24 h treatment of HepG2 cells

$O_2^-$ production (% of control / mg protein)

tGSH (nmol / mg protein)
Reactive oxygen species and glutathione levels

24 h treatment of HepG2 cells
Conclusions

• *In vitro* hepatotoxicity of the polycyclic aromatic NPS (6-APB, naphyrone) is increased compared to MDMA

• Some cathinone NPS (methylone, mephedrone, methedrone) may be less hepatotoxic than MDMA

• Pyrovalerone NPS (MDPV, naphyrone) may lead to mitochondrial dysfunction