Tobacco dependence – more than just the devil we think we know

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Smoking is reputed to be one of the hardest addictions to give up, yet in animal behavioural tests nicotine is not very addictive.

There are social, marketing and behavioural pressures which add to nicotine’s ability to “hook” people into smoking.

Nicotine is thought to have cognitive effects, where the associative component of dependence could be stronger for nicotine than for other drugs.

The inhalation route provided by smoking is key to nicotine’s effects.

But if nicotine is so addictive, why have people not found a way to abuse the nicotine in NRT?
Explanations?

Social/peer/advertising pressure.

The rituals around smoking are highly reinforcing in themselves.

The inhalation route gives a more rapid rise in nicotine concentration and this is key to nicotine’s addictive effect.

The time course over which rats are used in experiments is not long enough to fully mimic human smoking behaviour.

Are these explanations enough?

There is more in cigarette smoke than “just” nicotine. Over 5000 different chemicals.

We asked: is there an additional chemical component(s) adding to nicotine’s addictiveness?
Monoamine oxidase inhibitors are strong candidates

MAO activity is strongly inhibited in smokers. MAO breaks down dopamine:

Thus if MAO activity is reduced, once nicotine causes a dopamine reward, that reward should be more prolonged and be more reinforcing than is the reward from nicotine alone.

A cigarette with nicotine plus MAO inhibitors could be more “satisfying” and more addictive than one with the same nicotine but less MAO inhibitors.
From Amy Lewis’s PhD work: At the same nicotine content (same stimulus) roll-your-own tobacco had more MAO inhibitory activity than packet cigarettes, regardless of brand.
If RYO cigarettes have higher MAO inhibitory activity, are they more addictive?

Predictions:
1. People who smoke RYO’s should have lower quit success rates

   Yes - Quitline analysis.
   Li et al. (2010) NZ Med. J. 123, 64-73

2. People who smoke RYO’s will have higher dependency scores.

   Yes – MoH funded study
   Lea & Truman: Client Report FW 10004

Is this an association or does the higher MAO inhibition CAUSE the increased dependency?

We do not know
It's a rather interesting phenomenon. Every time I press this lever, that post-graduate student breathes a sigh of relief.
First, catch your tobacco smoke!

THEN - SELF ADMINISTRATION EXPERIMENTS:
Animals were trained to self-administer nicotine or saline TPM on training dose of 30 µg nicotine per kg body weight per infusion.
Tests were performed at 4 different nicotine doses, recording the number of responses per 2 hour session.
Results

1. Antagonist testing

Nicotine and TPM self-administration were very similar in many respects, suggesting that reinforcement is primarily a response to the nicotine in TPM, and its effects in the brain.

However, antagonist testing showed that the pathways of reinforcement within the brain were subtly different.

Ketanserin; serotonin receptor antagonist (0 or 2 µg/kg)

Results

2. Breakpoint testing

Breakpoint – measures how hard an animal will work for a drug reward

Breakpoint testing compared self administration of TPM from cigarettes and from RYO tobacco with self administration of nicotine.

The results showed that one brand of tobacco TPM, at least, was significantly more addictive than nicotine in this test.

<table>
<thead>
<tr>
<th>Nicotine dose 30 µg/kg/infusion</th>
<th>Breakpoint (±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>11.1 (± 1.0)</td>
</tr>
<tr>
<td>Cigarette TPM</td>
<td>14.2 (± 3.2)</td>
</tr>
<tr>
<td>Tobacco TPM</td>
<td>18.6 (± 1.7)</td>
</tr>
</tbody>
</table>

Results

3. Acquisition

A third difference was in acquisition of self-administrative behaviour.

As an example:
In a group of 23 rats taught to self administer nicotine, 8 had not acquired self-administrative behaviour after ten days. However, all but two were self-administering nicotine after 25 days of training, leading up to breakpoint testing.

In an equivalent group of 16 rats taught to self-administer TPM from RYO tobacco all were self administering the TPM after ten days and continued to do so over the course of the experiment.
The pathways for reinforcing addictive behaviour in the brain differ between tobacco smoke and nicotine.

Nicotine does not act alone in causing addiction to tobacco smoking, though it is the main addictive agent.

Different tobacco products may differ in their addictiveness, with Drum RYO tobacco being more addictive than Holiday cigarettes in these tests.

Three types of observation

Antagonist testing  Breakpoint testing  aCquisition

Cigarette TPM  RYO TPM > cigarette TPM
E-cigarettes – what can we learn from them?

1. Evidence from trials is that measures of dependence decrease when people switch to using E-cigarettes (Bullen, pers. comm.)

2. Evidence from surveys is that E-cigarettes are less addictive than are tobacco products (Etter et al., Drug and Alcohol Dependence, 2015)

3. Evidence from youth initiation is that youth trying E-cigarettes go on to established usage less often than young people trying tobacco smoking (C Gartner, pers. comm.)

The evidence thus far is that E-cigarettes are significantly less addictive than tobacco.
The working concept:

Nicotine causes responses which activate the brain’s reward system and cause the “I want more of this” behavioural response.
Nicotine

↓

Dopamine response

BUT Compound “X”

↓

An enhanced dopamine response using additional or strengthened pathways
The additional compound(s) are just one part of a complex physiological and psychological matrix that acts together to reinforce dependence on tobacco.
What chemicals could be responsible?

Nicotine analogues: nornicotine, anabasine, anatabine, myosmine and cotinine

Monoamine oxidase inhibitors (and acetaldehyde)

Something completely different?

We have seen three effects.
Are they manifestations of the same thing?
Or different?

One chemical?
One type of chemical or activity?
More?

We do not know (yet)
Monoamine oxidase inhibitors seem the most likely to act by a mechanism different from that of nicotine. They fit the profile.

There are several known MAO inhibitors in tobacco smoke.
BUT

Harman and norharman are reversible inhibitors with half lives lower than that of nicotine, so they should be cleared faster than nicotine is.

Plasma concentrations of harman and norharman are less than 2 nM, and their Ki’s are; harman 55 nM against MAO-A and norharman 730 nM against MAO-B; quite a lot lower than the concentration required to cause the 30-40% inhibition of MAO inhibition seen in smokers.

When smokers stop smoking MAO enzyme activity remains low for several weeks, long after the nicotine has cleared.

How could harman and norharman possibly cause the strong inhibition of MAO inhibition seen in smokers?
We saw big variations in responding between individual rats that were self-administering nicotine alone.

That variability was not seen for rats self-administering nicotine with harman and norharman added.

We saw no difference in breakpoint.

**WORKING HYPOTHESIS:** Inhibition of MAO activity by harman and norharman stabilises responding to nicotine.
Tentative conclusions

Harman and norhmarman may have behavioural effects. Unless they are actually irreversible inhibitors, or have some mechanism to build up in the brain and body by 20 to 200-fold or more (greater than the 3-10 fold suggested by other workers) they cannot cause the reduction in MAO activity observed in smokers. This has not yet been shown.

There may be other mechanisms at work,

but

- the other inhibitors in tobacco smoke deserve further attention.
Currently around 600,000 New Zealanders smoke. Half of all smokers are believed to die from smoking-related illnesses, losing on average 10 years of life. 80% of current smokers say they want to stop. Some people quit easily but on average it takes around 8 serious attempts before people actually stop for good. People need better help to stop smoking.
Recovery

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Tom Hume
maybe we can remove (or USE) one of the props that sustain smoking - potentially helping more people stop smoking.

And more kids will grow up knowing their grandparents
Thank you for your attention

Questions?