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Review article

Cardiovascular toxicity of novel psychoactive drugs: Lessons from the past

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ABSTRACT

The long use of ephedrine, amphetamines, cocaine, LSD and more recently 3,4-methylenedioxy-N-methylamphetamine (MDMA; "Ecstasy") allows us to predict with some confidence what cardiovascular risks are likely to be associated with novel psychoactive substances (NPS). Once the probably multiple biological activities of a compound are known it is possible to define the likely risks of cardiovascular toxicity. Agonists of 5-HT_{2A} receptors or alpha-adrenoceptors may cause vasoconstriction and tissue ischemia. Drugs which have agonist affinity for 5-HT_{2B} receptors will probably promote heart valve fibrosis leading to heart failure. Compounds that interfere with uptake of dopamine or 5-hydroxytryptamine (5-HT) are likely to also have effects on noradrenergic neurotransmission and lead to sympathomimetic effects on the heart and vasculature. Drugs that cause dopamine release, or inhibit uptake are likely to be addictive and lead to chronic use. Other drugs (particularly the so-called empathogens) are associated with weekly usage in social settings; over time such use can lead to cardiovascular harm. Defining which of these effects NPS have is an important element of predicting the harm they may cause and informing those appointed to introduce regulations to control them.

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1. Introduction

Several classes of recreational drugs that are taken primarily for their diverse effects on the central nervous system have additional effects on the heart and vasculature which contribute to morbidity and mortality. Illicit drugs such as cocaine and amphetamines which have a long history of use/abuse are clearly associated with increased risks of cardiovascular complications such as myocardial infarction and stroke (see below). Indeed, the use of some licit drugs with similar mechanisms of action – such as pseudoephedrine – are also associated with cardiovascular risks and dispensed with caution. There is now a subset of recreational drug users who shy away from illicit drugs, seeking alternatives which are legal only because they are sufficiently novel to not have been considered for regulation by authorities (Hill and Thomas, 2011). Apart from user reports (of uncertain veracity), the pharmacological and toxicological properties of some of these compounds are virtually unknown. Structurally novel 'legal highs' (or novel psychoactive substances; NPS) are appearing at a rate of 20 or more per year (European Monitoring Centre for Drugs and Drug Addiction, 2011). The unknown pharmacodynamic, pharmacokinetic and toxicological properties of such compounds represent a significant challenge to authorities tasked with preventing public harm. The speed with which purveyors of such compounds identify

Abbreviations: 2-CB, 4-bromo-2,5-dimethoxyphenethylamine; 5-MeO-DIPT, 5-methoxy-*N*,*N*-diisopropyltryptamine; 5-HT, 5-hydroxytryptamine; BZP, benzylpiperazine; CNS, central nervous system; DAT, dopamine transporter; LSD, lysergic acid diethylamide; mCPP, 1-(3-chlorophenyl)piperazine; MDMA, methylenedioxymethamphetamine; MDPV, methylenedioxypyrovalerone; NET, noradrenaline transporter; NPS, novel psychoactive substance; SERT, serotonin transporter; TCB-2, (4-bromo-3,6-dimethoxybenzocyclobuten-1-yl) methylamine; TFMPP, 1-(3-trifluoromethylphenyl)piperazine.

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and produce novel substitutes after regulations are put in place is a further challenge in this field. In this review we outline some of the aspects of NPS cardiovascular toxicity that might be predictable, based on our understanding of drugs with similar mechanisms of action.

The cardiovascular effects of recreational drugs are – to some extent – predictable because the receptors and transporters on which they act are located both in the central nervous system and in the periphery. There is a limited palette of molecular targets in the central nervous system upon which drugs that produce the varied desired effects can act. Some classes of drugs are unlikely to have a vascular risk profile and are not considered in depth in this review. For example, cannabinoids produce a predominantly vasodilator response (Randall et al., 2004), and are unlikely to cause cardiovascular complications. Others, acting on serotonergic, dopaminergic or noradrenergic systems are far more likely to induce vasoconstriction and/or tachycardia and arrhythmia. The most hazardous compounds are likely to be those that have some central dopamine-releasing activity – carrying higher risks of addiction and chronic abuse – combined with peripheral cardiovascular effects which are likely to be toxic after such continued abuse. We have experience with a sufficient number of licit and illicit drugs to be able to assess – with some confidence at least – what the potential risks of NPS might be once their pharmacological activities are characterised. Because these drugs often share structural similarities with several such bioamines, their effects are rarely limited to a single receptor or transporter. Hence it is difficult to decide whether, for example, some of the hallucinogenic amphetamines should be characterised as hallucinogens or CNS stimulants, phenethylamines or tryptamines. We have structured this review around the different endogenous signalling systems, rather than classes of chemicals, or the potentially mixed effects they have on the body to simplify an assessment of the cardiovascular risks that might be predicted for molecules with mixed affinities and efficacies.

2. Serotonergic drugs

Serotonin (5-hydroxytryptamine (5-HT)) takes its name from the vasoconstrictor effects it was first reported to elicit. It was originally discovered as a platelet-derived vasoconstrictor factor (reviewed by Green, 2008; Watts, 2002) and it was some years before its role as a central nervous system neurotransmitter was described (Green, 2008). The bulk of the 5-HT present in the body is stored in gastrointestinal entroerchromaffin cells which release 5-HT when triggered by a variety of stimuli. Some of the spillover of 5-HT is taken up and stored by platelets, which possess the same uptake mechanisms as neurons, the other significant source of 5-HT in the body. It is probable that the physiological role of vascular 5-HT receptors is to mediate vasoconstriction to support a clot and limit blood flow. Activation of this system throughout the body has a profound vasopressor effect. Indeed, 5-HT induced vasospasm has been implicated in the pathogenesis of circulatory disorders such as migraine and Raynaud's phenomenon (Kaumann and Levy, 2006). Unsurprisingly, 5-HT receptors were for a long time considered to be a potential target for novel hypertensive drugs. Indeed, the 5-HT_{2A} receptor antagonist ketanserin was an effective antihypertensive, but was withdrawn due to associations with torsade de pointes (Nagatomo et al., 2004). Similar antagonists with fewer cardiac effects have been produced, but have been surpassed by other classes of anti-hypertensive agents and have more limited indications.

The history of ergotism warns of the potential cardiovascular risks of serotonergic agents (Haarmann et al., 2009). The fungus *Claviceps purpurea*, which has periodically infected cereal crops over the centuries, contains a variety of alkaloids which act at bioamine receptors, particularly 5-HT receptors (Schiff, 2006). Ingestion of bread made from infected crops produced profound peripheral vasoconstriction that underscored all of the pathological signs of what came to be known as St Anthony's Fire. Victims writhed from the pain of the extensive ischemic damage to their extremities and many ultimately died. Later, ergot preparations came to be used medicinally for inducing abortions and later for preventing post-partum bleeding when the uterus fails to contract sufficiently. One constituent of ergot, ergometrine, is still occasionally used for this purpose today (Basket, 2000; Basket, 2004) and there have been occasional reports of iatrogenic ergotism in the literature (e.g. Ibrahim et al., 2008), despite the relative selectivity of this compound for uterine over vascular smooth muscle. Ergometrine has also been used for many years – and with caution – as a provocation test for coronary artery vasospasm (Siegel, 2010). The precise receptor pharmacology of ergometrine is uncertain — the compound has affinities for receptors for 5-HT as well as those for catecholamines. It is not surprising then, that NPS which have 5-HT agonist properties have the potential to harbour similar, additional cardiovascular risks.

There are at least 14 receptors for 5-HT, but the two main receptors expressed by vascular smooth muscle are 5-HT_{2A} and 5-HT_{1B} (see Kaumann and Levy, 2006). The relative contributions of each receptor vary between vascular beds. For example, the high expression of 5-HT_{1B} receptors by cerebral arteries was the original target of the 'triptan' class of drugs (5-$HT_{1B/D}$ agonists) which are used to promote vasoconstriction in migraine, but also activate 5-HT_{1F} receptors on perivascular nerves (Mehrotra et al., 2008). Since the coronary circulation has a less significant population of 5-HT_{1B} receptors, with 5-HT_{2A} predominating, this class of drug is relatively free of coronary side-effects. However, triptans are generally prescribed with caution in patients with underlying heart conditions because of the possible risk of coronary vasoconstriction and this may be why they appear to have a good safety profile (Bigal et al., 2009). The pharmacology of an older (but still utilised) drug for migraine makes an instructive example of the complicated nature of cardiovascular 5-HT receptor pharmacology. Methysergide was originally introduced as a 5-HT antagonist to prevent what was considered the dominant role of 5-HT in migraine pathogenesis. Though still considered a 5-$HT_{1/2}$ antagonist to this day, it seems likely that the active – and more potent and efficacious (Roon et al., 1999) – metabolite (methylergometrine/methylergonovine) mediates the beneficial effect of this drug possibly via agonist activity at 5-$HT_{1B/D}$ or 5-HT_{1F} (Adham et al., 1993) receptors. CNS side-effects of methysergide (mild hallucination upon initial dosing is not uncommon) have always been a problem with its use in migraine prophylaxis; in the 1950s and 1960s it was found that methysergide was only 175 times less potent than LSD (the parent molecule) at producing similar CNS effects (Abrahamson and Rolo, 1965). Although the pharmacology of this compound has never been fully resolved, the activity of methysergide as a 5-HT_{1A} agonist (Newman-Tancredi et al., 1997) probably accounts for some of its CNS activity. The potent hallucinogen LSD, on the other hand, appears to act as a partial agonist of both 5-HT_{2A} and 5-HT_{1A} receptors (Halberstadt and Geyer, 2011; Passie et al., 2008), with effects via 5-HT_{2A} receptors predominating. In selecting NPS, many vendors appear to mine the scientific literature for potential 5-HT_{2A} agonist hallucinogens (e.g. 5-methoxy-*N*,*N*-diisopropyltryptamine (5-Meo-DIPT); Shulgin and Carter, 1980), with little consideration for what other properties these molecules may have. For example, 5-methoxy-*N*,*N*-diisopropyltryptamine (5-MeO-DIPT; "Foxy") elicits behavioural effects in animals similar to LSD via binding to 5-HT_{2A} receptors, although this compound has higher affinity for 5-HT_{1A} receptors (Fantegrossi et al., 2006), and also inhibits 5-HT uptake by blocking the 5-HT transporter SERT (Nagai et al., 2007; Sogawa et al., 2007). Similarly, there has been a recent increase in the use of fairly non-selective phenylpiperazine 5-HT agonists such as 1-(3-chlorophenyl)piperazine (mCPP) and 1-(3-trifluoromethylphenyl)piperazine (TFMPP) (see Arbo et al., 2012; Hill and Thomas, 2011), which have been used experimentally for some decades (e.g. Lucki et al., 1989) and are now thought to also act via the SERT (Baumann et al., 2004; Eriksson et al., 1999). These rather old piperazine compounds – once potential anti-migraine drugs (Curzon and Kennett, 1990) – have such mixed affinities for 5-HT receptors and bioamine transporters that they