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Abstract

Idiopathic environmental intolerance (IEI) is a medically unexplained disorder characterised by a wide variety of unspecific symptoms in different organ systems and attributed to nontoxic concentrations of chemicals and other environmental factors that are tolerated by the majority of individuals. Both exposure to chemicals and behavioural conditioning are considered as possible contributors to the development of IEI. However, owing to the heterogeneity of the condition, it is difficult to separate the toxicological, physiological and psychological aspects of IEI. Here, we review the evidence for postulated toxicologically mediated mechanisms for IEI. Available data do not support either a classical receptor-mediated or an idiosyncratic toxicological mechanism. Furthermore, if there were convincing evidence for a psychological cause for many patients with IEI, then this would suggest that the priority for the future is the development of psychological treatments for IEI. Finally, we advocate genome wide screening of IEI patients to elucidate genotypic features of the condition.

Keywords

Idiopathic environmental intolerance, toxicological, mechanism, psychological

Introduction

Idiopathic environmental intolerance (IEI), formerly called Multiple Chemical Sensitivity, is a medically unexplained disorder associated with environmental exposures and remains a potentially disabling condition in sufferers.[1–4] A systematic review of the published literature published in 1999 concluded that there was no unequivocal epidemiological evidence for IEI, although the collated evidence suggested the existence of IEI.[5] IEI is extremely difficult to study as a toxicological phenomenon for a number of reasons. First, there are no internationally accepted diagnostic criteria and it is very difficult to assess the reliability of the published diagnoses of IEI. There are many published case definitions based on a diagnosis of exclusion of other related conditions using assessment of symptoms with evidence for multiorgan response, the duration of the condition and evidence for chemical exposure triggered symptoms.[2,4,6–8] A number of published approaches to diagnosis use structured questionnaires to assess reported symptoms that have improved study comparison.[4,7,8] However, there is no accepted biological or physiological test for IEI.[9–11] Many studies purporting to provide information on IEI were undertaken with individuals with closely related conditions such as chemical intolerance, sensory hyper-reactivity and cacosmia, and in some instances, studies have been undertaken using patients with self-reported IEI (sIEI), also referred to as IEI symptomatics.[12–15] The second aspect that complicates a toxicological evaluation of the literature is that a wide range of nonspecific symptoms are reported by patients with IEI. These symptoms are related to effects on multiple target organs and attributed to a vast range of chemical exposures.[2] The American Academy of Allergy and Clinical Immunology reported that the list of environmental

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exposures triggering symptoms in patients with IEI was virtually unlimited.[16] Examples of IEI have been reported for diverse chemicals such as perfumes, cleaning solvents, fresh paints, air fresheners, pesticides, car exhausts and exposure situations such as at the hairdressers, visiting public parks, passive smoking and exposure to barbeque grill smoke.[17,18] A US population survey of chemical intolerance involving 1582 individuals (199 with unusual sensitivity to chemicals and 49 with clinical diagnosis of IEI) reported a wide range of potential trigger exposures with pesticides and solvents being reported as the most common claimed original causes (19 individuals from 97 who reported information on first exposures).[17] Miller reported 119 symptoms in a report on 112 individuals who were reported to have chemical intolerance.[19] Lacour and colleagues undertook a systematic review of symptoms and target organ systems for 777 sIEI patients. The results, which are consistent with other investigations, identified the following target organ systems in patients with sIEI (in order of prevalence): central nervous system (CNS), musculoskeletal, gastrointestinal, dermal, auditory, mucosal and respiratory, polyneuropathy-like and cardiovascular.[2] From these data, it can be concluded that a key consideration for defining IEI is sensitivity to a wide variety of chemical structures with resultant effects on a range of organ systems. This forms a basis for the research in the mechanism of IEI in response to chemical exposure.

A further aspect complicating the assessment of potential toxicological mechanisms for IEI is that IEI patients present with abnormal psychology. Thus, high rates of somatoform disorder, the conversion of mental state into physical symptoms are reported in IEI.[11] A cross-sectional study of 732 self-reported or physician-diagnosed IEI patients using questionnaires and regression analyses found a significant positive association between IEI and a range of abnormal psychological processes, including negative affectivity, and a small inverse association with the personality trait of absorption, the predisposition to be immersed in sensory information.[20–22] The finding of absorption was confirmed in a smaller study of 54 IEI patients.[23] Experimental work has shown that individuals can learn to develop adverse physical symptoms of the type reported by IEI sufferers when odours or mental images are paired with a stimulus capable of producing those symptoms.[24–30] Furthermore, they demonstrate that once this learning has taken place, exposure is not required as an explanation for future reoccurrence of these symptoms. This phenomenon occurs in cancer patients awaiting their second and subsequent chemotherapy, who can develop an anticipatory nausea and supports the classical conditioning model.[31] Several factors have been related to the attribution of symptoms to an environmental trigger and development of IEI including the individual's focus of attention, in terms of both priming an individual to expect adverse symptoms and in deliberate distraction during symptom learning, their expectations and beliefs, negative affectivity and psychiatric disorder.[23,32–39]

A systematic review of provocation studies considered 37 studies involving a total of 784 subjects with sIEI, 547 controls and 180 individuals of whom a subset were described as chemically sensitive.[39] The authors concluded that sIEI patients do react to chemical challenges; however, these responses occur only when they can discern differences between active and sham substances.[39] In a recent report of exposure to odourants and blank stimuli, the response of a patient with IEI regarding odour intensity was related to prior information regarding whether or not the odour was harmful.[40] In addition to abnormal psychology, a significant overlap of symptoms between IEI and chronic fatigue syndrome (CFS), primary fibromyalgia, sick building syndrome, sensitivity to electromagnetic fields (IEI–EMFs) and Gulf War Syndrome has been reported.[2,11,41,42] Reid and colleagues evaluated British Gulf War veterans and concluded that IEI and CFS account for some of the medically unexplained illnesses reported by veterans deployed to the Gulf.[43] A review of 46 blind and double-blind provocation studies involving IEI–EMF volunteers reported no robust evidence for exposure to EMFs and the triggering symptoms of IEI–EMF but did support the role of a nocebo effect in IEI–EMF sufferers.[44] Another review of 29 single- or double-blind provocation studies found that there was no reliable evidence to suggest that individuals with IEI–EMF experience unusual physiological reactions as a result of exposure to EMFs.[44] Overall, these data show that IEI is a complex multifactorial condition and consequently it is difficult to distinguish toxicologically mediated aspects of IEI from the psychological aspects of the condition. In addition, IEI patients have been reported to have a high incidence of allergic disease that is likely to confound any diagnosis of IEI.[4]

Many patients with IEI make significant changes to life style to avoid exposure to chemicals.[45] It would be inappropriate from a public health perspective to encourage such avoidance behaviour if there were no

toxicologically mediated mechanism(s) of importance to the aetiology of IEI. Alternatively, if a toxicologically mediated mechanism was relevant, this would add weight to the evidence regarding the assessment of cause and effect. There are relatively few reviews available regarding the proposed toxicological mechanism relating to IEI.[5,46–48] The approach taken in this review differs from the available published reviews in that the evidence has been assessed against two widely accepted general theories of toxicological mechanisms: (1) whether the evidence proposed for postulate mechanism/mechanisms is consistent with classical toxicological principles, which are evidence for dose–response, receptor-mediated effects and evidence for a threshold and reversibility or (2) a potential toxicological idiosyncratic reaction, defined as an abnormal reaction to a drug owing to an inherent, frequently genetic, anomaly.[49] In the case of toxicological idiosyncratic reactions, there is a need to provide a biological rationale for the observed effects, for example, drug-induced idiosyncratic effects involving immune-mediated effects, polymorphisms of drug metabolism, low-level inflammatory reactions and drug-induced mitochondrial toxicity.[50,51]

Any proposed mechanism would also have to be consistent with response to a large range of chemicals at doses below those that cause any response in the majority of the population. In addition, there is a need to explain the phenomenon of generalisation, the process whereby IEI patients respond to an ever increasing range of chemicals. The evidence retrieved for proposed mechanisms for IEI reported in the scientific literature up to January 2012 has been divided into seven categories according to organ system or type of mechanism for ease of review. A number of proposals attempt to explain IEI in terms of multiorgan response. Thus, reviewers have suggested the existence of CNS–immune system interaction.[52] Other reviewers have proposed that the concept of an 'integrated defense system' can form the basis of a disease model for IEI, where CNS, immune and endocrine systems all respond to give rise to the condition.[53] The evidence-based approach used for this review incorporates such multiorgan proposals.

Evidence for the mechanisms involving organ systems

Altered odourant threshold

Heightened olfactory threshold sensitivity has been noted as one possible mechanism underlying the response of individuals with IEI to chemicals.[46] Ross and colleagues reported in their review of IEI that nearly all IEI symptomatics complain of altered odour sensitivity.[54] However, the available studies of odour detection in individuals with clinically diagnosed IEI do not reveal any differences in odour thresholds: phenyl ethyl alcohol (PEA),[55–57] *N*-butanol,[8,58,59] methyl ethyl ketone,[55] pyridine,[57] odour discrimination[8] or odour identification with a wide range of common odourants[8,57,58,60] when compared with control subjects. In a limited number of studies using 1-octanol, isopropanol, 2-ethylhexanol and pyridine, chemosensory symptoms are similar in individuals with heightened sensitivity to odourants compared with controls.[57,61,62] However, most studies identified report that odour intensity, irritancy, annoyance, perception as unpleasant, pungency and nauseating effects are significantly higher in individuals with self-reported higher chemical sensitivity or patients with clinically diagnosed IEI.[57–61,63] One proposal reported that differences in cognitive processing by IEI patients compared with controls could explain both these results and the reports of heightened olfactory response to chemicals in IEI patients.[54,56]

A small number of studies have reported objective investigations of olfactory response in subjects with IEI. Hummel and colleagues measured chemosensory event–related potentials (CSERP) in 23 IEI patients (defined according to Cullen's criteria).[56] The subtle changes in CSERP seen in these IEI patients as decreased CSERP latency with 2-propanol was significant for positive peak number 1 (T-P1) and negative peak number 1 (T-N1). These were considered to involve early stages of information processing of exogenous stimulus characteristics such as perceived stimulus intensity or the attention it received. The authors noted the need for additional studies to compare IEI patients and healthy controls. Papo and colleagues undertook a similar study of CSERP in 23 IEI patients and healthy control subjects (21 with odour sensitivity and 23 without odour sensitivity).[58] The results of CSERP analysis did not support a hypothesis of alterations in cognitive processing in IEI, although IEI patients perceived olfactometry more negatively than control groups. Overall, the authors concluded that neither olfactory functions nor chemosensory or cognitive olfactory information processing are impaired in IEI patients. An investigation of positron emission topography was undertaken in 12 IEI patients (diagnosed according to World Health Organisation consensus criteria 1999), and 12 age-

matched controls who smelled a range of odours including vanillin (olfactory stimulant), acetone (trigeminal stimulant), four odourants (cedar oil, lavender oil, eugenol and butanol) and two putative pheromones.[59] The authors commented that IEI patients showed reduced rather than enhanced activation of cerebral regions processing odour signals, which was inconsistent with the concept of sensitisation of olfactory regions. During several exposure conditions, IEI patients but not controls activated the anterior cingulate and precuneus cuneus. These data were considered to be consistent with altered odourant processing by IEI patients and in particular top-down regulation via the cingulated cortex. One suggestion was that this represented 'harm avoidance' reaction in IEI patients.[59] A study has been undertaken to ascertain whether clinically diagnosed IEI patients present brain single photon emission computed tomography and psychometric scale changes after a chemical challenge.[64] After the chemical challenge, IEI patients exhibited dysfunction, particularly in those areas involved with odour processing. The cases had poorer neurocognitive function at baseline, which worsened after chemical exposure.[64]

Thus, the available objective studies report consistent evidence of odour intolerance to a wide range of chemicals and suggest that there is no altered odour threshold associated with IEI and that odour annoyance in the small number of IEI patients who have been studied could involve altered cognitive processing of odours. These data do not suggest either a receptor-mediated or an idiosyncratic response.

Primary or trigeminal irritancy of upper airway

There is considerable evidence to support heightened annoyance reactions and sensory irritation associated with the diagnosis of IEI.[57–61,63] Patients with IEI have also been reported to exhibit a more rapid onset and accumulation of sensory irritancy compared with controls.[65,66] An exaggerated vanilloid receptor activation response has been proposed as a possible mechanism for IEI.[67] Meggs proposed the term 'neurogenic inflammation' in relation to IEI referring to chemically mediated activation of c-fibres leading to the release of vasodilator neuropeptides.[68,69] There is evidence from studies using human volunteers with IEI, both clinically diagnosed and self-reported, and individuals with the related disorder 'sensory hyperreactivity' and from one animal model to suggest that vanilloid receptor activation is at least partly responsible for some of the symptoms reported in some IEI patients. Increased capsaicin cough sensitivity has been documented in two small studies of clinically diagnosed IEI patients versus eczema patients with airway symptoms elicited by odourous chemicals, where it correlated with the presence of lower airway symptoms irrespective of clinical diagnosis, and in a small group of patients with sensory hyperreactivity.[13,70–72] Overall, 25 patients with sIEI (13 women/12 men, aged 33 $\pm$ 7 years), 25 patients with atopic eczema/dermatitis syndrome (AEDS; 13 women/12 men, aged 33 $\pm$ 7 years), 25 controls (13 women/12 men, aged 31 $\pm$ 6 years were exposed to a mixture of volatile chemicals derived from painted surfaces of a room. Plasma substance P, vasoactive intestinal peptide and nerve growth factor were measured before and after exposure for 15 min, whilst individuals watched a video. Increased levels of these parameters were reported in the sIEI patients compared with patients with AEDS or controls.[15]

Anderson and Anderson reported exposure of mice to mixtures of air emitted from air fresheners, fabric softeners and mattresses.[73] Air concentrations of fabric softener were approximately 250 ppm (mixtures of volatile organic compounds measured by flame ionisation detector (FID) based on 100 ppm methane as calibration). Concentrations of volatile organic compounds from other sources were not reported in the publication retrieved for this review. Evidence for sensory irritation measured by whole body plethysmograph was reported for all samples studied. The authors noted evidence for increased sensory irritation with duration of exposure for one particular brand of fabric softener, several brands of vinyl mattresses and certain brands of disposable diapers. This was considered to represent the sensitisation of mice to certain mixtures. The authors suggested that this may be a model for the development of increasing sensitivity to environmental pollutants. The authors also reported that air taken from rooms where solid air freshener had been hung or derived from laundry treated with fabric conditioner could also induce sensory irritancy (SI), plus evidence for pulmonary irritancy and some neurotoxicity. Additionally, it was reported that air from a Federal Office building captured in a Teflon bag induced respiratory depression in mice.[73]

These data provide limited evidence for exaggerated vanilloid response in small number of patients with IEI, some with clinical diagnosis and some self-reported, but there are no controlled blind studies to show a vanilloid response in the absence of knowledge of

exposure. The available data do not explain how patients with IEI can respond to a very large range of chemicals, and the studies did not control for the occurrence of asthma. The proponents of sensory irritancy as a mechanism for IEI consider additional receptor targets in the trigeminal nerve system for volatile organic compounds other than transient receptor protein subfamily V number 1 (TRPV1) or transient receptor protein subfamily A number 1 (TRPA1) (cold-sensitive neuron response). Thus, Inoue and Bryant reported responses to C5 pentanol, pentanal and pentenal may involve other, as yet unknown receptor systems.[74] It is therefore difficult to conceive a toxicological mechanism involving the vanilloid receptor that could account for the diversity of symptoms associated with IEI following exposure to levels of chemicals orders of magnitude below those required to cause adverse effects in most people. It remains possible that there is an interaction between a trigger effect of sensory irritancy and psychological aspects of IEI.

Immune system effects

The proposal that IEI is caused by chemically mediated immune dysfunction is one of the more widely cited potential mechanisms for IEI in the literature.[5,75] Investigators noted the evidence for inflammatory responses in patients, which implied that the immune system was involved.[76] The available publications are limited by the case definitions used, which vary between different reports, and the magnitude of effects documented, which have been reported to be clinically nonsignificant. Mitchell and colleagues reported on the variation between the available reports regarding diagnosis, use of controls, test selection, provision of data on normal range of indices, quality control and analytical methods used.[77] The available case–control studies report some effects on lymphocyte populations. For example, increase in percentage CD4+ in one study[78] and increased CD4+ and decrease CD8+ counts in a separate study.[77] Baines and colleagues reported evidence for lower lymphocyte count in a group of 223 IEI cases compared with 194 controls.[79] The cases were diagnosed using the self-administered questionnaire of University of Toronto Health Survey. The magnitude of the reduction was considered by the authors not to be clinically significant. These data do not provide convincing evidence for altered immune status in IEI, but the available investigations were limited. For example, subjects with allergic disease should have been clearly identified. A significant overlap between self-reported chemical intolerance and asthma or hay fever has been documented.[12] It is also difficult to conceive how the wide range of chemicals claimed to cause IEI could affect quite subtle pathways of immune dysregulation identified and thus overall there is no evidence for a toxicological receptor-mediated response.

Neurotoxic effects

Two hypotheses regarding IEI have been proposed. Corrigan and colleagues proposed that fatigue syndromes in general may be secondary to altered sensitivity of the gamma aminobutyric acid a receptor (GABAa) receptor giving rise to impaired concentration, lethargy and increased sensitivity to alcohol, and that this is secondary to the effects of organochlorine compounds in the CNS.[80] Part of the hypothesis involved mobilisation of organochlorines from adipose tissue following viral infections. It was also postulated that organophosphate effects on the cholinergic system might interact with gamma aminobutyric acid (GABA)ergic systems of the hippocampus with regard to fatigue syndromes. The hypothesis appears to have been developed on observations from five case histories.[80] There were no objective investigations of GABA system functions in subjects with clinically diagnosed IEI retrieved to support this hypothesis. In the second hypothesis, Overstreet and colleagues observed that many characteristics of the Flinders Sensitive Line (FSL) rats overlapped with IEI and/or depression; for example, effects on food craving, sleep disturbances, loss of drive, reduced activity, cognitive disturbances and a gender ratio with excess responders in females compared with males. In addition, the FSL rats were more responsive compared with Flinders Resistant Line rats (FRL) or open bred strains with regard to a wide range of pharmacological agents including anticholinesterase inhibitors, muscarinic agonists, dopamine D1-like family / D2-like family (D1/D2) agonists, 5-hydroxytryptamine (5-HT) agonists, benzodiazepine agonist (diazepam) and ethanol with regard to hypothermia and/or activity. FSL rats also exhibited greater bronchoconstriction in response to cholinergic and allergen-induced bronchoconstriction. FSL rats had elevated levels of muscarinic receptors compared with FRL rats. It was suggested that the multiple mechanisms underlying the chemical sensitivity of FSL rats, in particular cholinergic hypersensitivity,

might provide useful insight into the mechanisms of IEI.[81–83] No specific studies of FSL rats following exposure to environmental chemicals were retrieved for this article. IEI is reported by affected individuals to be associated with exposure to very low levels of a wide range of chemical exposures and this would appear to be inconsistent with the receptor-mediated neurotoxic effects reviewed in this article. Neither of the two hypotheses advanced can account for the diversity of chemical triggers for IEI.

Time-dependent sensitisation (TDS)

A significant amount of research has investigated the phenomenon of TDS. TDS is reported to be the amplification of subsequent responses to a novel or foreign and potentially threatening stimuli by the passage of time between the initiating and subsequent perpetuating stimuli.[84] This would go some way to explain the process of generalisation, whereby IEI patients respond to an increasingly wide diversity of chemicals with time. A further aspect of the TDS and kindling hypotheses is the potential for cross-sensitisation between classes of stimuli leading to the generalisation and response to a diverse range of chemicals. Kindling is a special form of TDS involving the olfactory–limbic system. Kindling is distinguished from TDS in that it involves convulsive or subconvulsive end points in limbic structures, whilst sensitisation involves a wider range of behaviours and physiological responses.[84] The model of IEI proposed by Bell and colleagues involves kindling in the olfactory bulb, amygdala and piriform cortex as well as hippocampus. Kindling could explain the potential amplification of response to low levels of chemical exposure and the potential for responses to a wide range of chemicals. An important part of the argument relating kindling in the olfactory bulb, amygdala and hippocampus to the development of IEI is the manifestation of IEI includes somatic dysfunctions regulated by these brain structures, for example, mood, spatial ability, memory, eating drinking, sexual dysfunction, stress responses, neuroendocrine and immune regulation.[14] In more recent reviews, Bell and colleagues have described neural sensitisation as having properties analogous to IEI, involving progressive host amplification of symptoms over time resulting from repeated intermittent exposure to stimuli, including drugs, chemicals, endogenous mediators and exogenous stressors. Potential useful outcome measures proposed by Bell and colleagues include electroencephalograph (EEG), blood pressure, heart rate and plasma β-endorphin.[85] The combination of exposure to nontoxic doses of chemicals with heightened amplification of responses via the olfactory pathway was proposed as a possible mechanism for the process of neural sensitisation. Subsequent activation of the limbic and mesolimbic pathways can then facilitate dysregulation of behavioural, autonomic, endocrine and immune system functions.[86] One outcome of the neural sensitisation process would be odour intolerance.[87]

A number of investigations have been published to support the TDS hypothesis, which used cacosmics as subjects who were rated on a chemical odour intolerance index (CII) as moderately intolerant. These individuals differ from IEI subjects in the severity of odour intolerance and do not exhibit multiorgan symptoms or changes in life style owing to exposure to chemicals. In these studies, self-reported illness in cacosmics was investigated using two populations, a young adult group of college students enrolling on a psychology course and an elderly group obtained from mail requests to individuals living in a retirement area and those already partaking in a study of osteoporosis.

Two health-based questionnaire studies were published using undergraduate students who also completed the CII.[88,89] The authors reported an association between cacosmia and limbic symptoms, which was still evident in the one study where the results for depression and anxiety had been considered. The authors hypothesised that CNS disruption in individuals with chemical intolerance might also be associated with quantitative EEG patterns (qEEG).[90] The study examined qEEG in young adults (undergraduate students) who were high/low in self-reported illness from chemical odours subdivided into those high/low on Symptom Checklist 90 revised (SCL 90r) for depression subscale during nose or mouth exposure to *n*-butanol, galaxolide or propylene glycol in filtered air. Overall, the authors reported that individuals who self-rated themselves as chemical odour intolerant exhibited differences qEEG at rest following specific tasks but no specific changes in qEEG were associated with chemical exposure in this study.[90] In a subsequent investigation, patterns of waking EEG were investigated in individuals with self-reported chemical odour intolerance.[91] This study differed from the previous studies in that individuals undergoing EEG assessment reported considerably more severe odour intolerance (>18/25 on CII scale) and life style changes in response to odours,

thus making them closer to a clinical diagnosis of IEI than the previous studies from this research group. Subjects were exposed in a double-blind scenario to galaxolide and propylene glycol on two separate occasions separated by 5–9 days and the session two data were compared with session one data for evidence of TDS. During the second session, the high-concentration galaxolide produced a significant increase in the delta EEG power measured at the CZ position in the chemically intolerant group. The authors considered the data were consistent with the hypothesis that individuals with intolerance to low levels of environmental chemicals sensitise their EEG responses to brief laboratory exposures over time.[91] However, it was reported that the subgroup with chemical intolerance and life style changes did not demonstrate any evidence for TDS. These individuals would have been expected to sensitise their EEG response more readily than individuals with chemical intolerance, who did not exhibit life-style changes.[91] One possible explanation for these data is that cacosmics simply learnt to respond to the odour from galaxolide.

In studies in elderly subjects, a higher incidence of allergic disease and irritable bowel disease was diagnosed in cacosmics.[14] There were no differences in depression, shyness, mastery and anxiety between the two groups. The authors argued that the development of cacosmia in elderly subjects in the absence of evidence for depression is consistent with a TDS-based mechanism.[14] A subsequent intervention study was undertaken using a small group of elderly cacosmics (mean CII suggested moderate cacosmia, 12/25 on CII index). Evidence for changes in plasma β-endorphin levels in response to baseline and milk diet intervention were interpreted as indicating hypothalamic–pituitary–adrenal stress response.[92] In a subsequent study using a milk diet intervention in elderly cacosmics, raised systolic blood pressure and pulse rate were measured at rising from sleep in cacosmics.[93] The authors argued that changes in blood pressure became evident over the time course of the intervention study, which was consistent with laboratory context-dependent sensitisation.[93] The studies in elderly cacosmics are difficult to interpret as evidence for IEI since there are few data available on the clinical features of IEI in elderly subjects, the particular cacosmics studied showed relatively moderate chemical intolerance compared with IEI patients, and the studies did not give consistent changes for the parameters measured during the intervention with milk diet. There are no similar investigations of TDS from other research groups.

To support the human studies, there is relevant information from animal models. Studies involving pharmacologically active compounds have reported behavioural sensitisation in rodents exposed to subconvulsive doses of pentylenetetrazole, 3,4-methyelenedioxymeth-amphetamine and nicotine.[94–97] Studies using environmental chemicals supporting TDS were retrieved using a number of pesticides (endosulan, dieldrin, lindane, chlordimeform, cismethrin and deltamethrin) using enhanced sensitivity to electrical kindling of the amygdale.[98–100] Other chemicals that have been cited in the literature include chlorpyrifos (behavioural effects in rodents), toluene (effects on locomotor activity and CNS functions) and formaldehyde.[101–108] Most data were available from studies using formaldehyde where rats were exposed to 1–3 ppm or 11 ppm formaldehyde for periods of 1–2 hours/day for periods of 7 days or 5 days/week for 2–4 weeks. Findings from these studies included enhanced cocaine-induced locomotor activity 4–6 weeks post-exposure, enhanced conditioned fear response to orange oil odour and reduced extinction of fear response and increased serum cortisol (conditioned anxiety response). These studies were suggested to indicate that conditioning to odours was relevant to the mechanism of IEI and that airway irritancy to formaldehyde may lead to stimulation of neural pathways leading to avoidance predominantly involving the hypothalamic–pituitary–adrenal axis. They considered that anxiety could not explain all of IEI symptomatology and noted that increased airway inflammation and a predisposition to amplify neural circuitry involved in pairing irritants and odours may be important. These studies on formaldehyde provide some evidence for integration of odour and irritant response in the aetiology of TDS, but there is no evidence for a dose-related effect in these studies (it is noted that serum cortisol was increased at exposure to 0.7 ppm formaldehyde but not 2.4 ppm). There are no other studies available with other chemicals at dose levels above or below the threshold for irritancy to confirm these observations. It is difficult to relate these findings to a model of IEI where challenge exposures eliciting symptoms are many times below exposures, which would result in irritant or toxicological effects.

The features of the TDS hypothesis of IEI do provide explanations for some of the observed clinical features of IEI, in particular, the generalisation in the

number of chemical triggers and rationale for multiorgan responses. However, the balance of evidence from human studies and animal models is insufficient to reach a conclusion that TDS owing to chemical exposure is a relevant mechanism for IEI since the available studies with human subjects did not use patients with IEI and the findings of studies were inconsistent. The animal models largely relate to dose levels of chemicals that were overtly neurotoxic. The studies using formaldehyde exposure provide some evidence where the irritant effects could induce overstimulation of neural pathways. However, this would still not explain why exposure to environmental chemicals below irritant thresholds could induce IEI in a small number of exposed individuals.

Other mechanistic hypotheses

There are a number of other proposed mechanistic hypotheses for IEI, which have been developed to account for the features of IEI but for which there is little evidence either from patients with IEI or related groups such as cacosmics or animal models.

Heightened sensitivity of the vomeronasal organ (VNO)

The proponents hypothesise that the response of the VNO to odourants in IEI is associated with induction of endocrine and neuronal responses. However, there is no evidence for a neural link with the VNO in subjects that have been examined and studies in subjects with or without the VNO and investigations, where the VNO covered showed no differences in odour detection, identification and threshold for PEA and androstenone.[109,110]

Elevated nitric oxide/peroxynitrite increased sensitivity of N*-methyl-*D*-aspartate (NMDA) receptors*

It has been proposed that chemical exposure increases nitric oxide and peroxynitrite in the nervous system resulting in enhanced NMDA receptor activity.[111] The author proposed that prolonged stimulation of NDMA receptors, particularly in the hippocampus would fit with the TDS hypothesis. The multiple feedback loops in the proposed mechanism would ensure that peroxynitrite levels once increased would remain elevated thus explaining the chronic nature of IEI. The hypothesis was also proposed to explain the overlap between IEI and CFS and other disorders such as post-traumatic stress disorder. The author proposed that chemical exposures that might induce this mechanism could involve organophosphates, carbamates and solvents. However, there is no direct evidence for this as a mechanism for IEI in either human studies or experimental animals. It is also difficult to conceive how the very wide range of chemicals cited as triggers for IEI could all lead to elevated nitric oxide.

Integrated defence system overlap as a disease model with examples for IEI

Rowat proposed that CNS, immune and endocrine systems communicate through common messengers.[53] Such responses included stress response, acute-phase response, nonspecific immune response, immune response to antigen, kindling, tolerance, TDS, neurogenic switching and traumatic dissociation. Several models of chemical exposure combined with psychological factors were outlined. The proposed hypothesis is that chemical stimulation of common messengers results in a diversity of effects, which could explain the diverse symptoms associated with IEI. The hypothesis does not explain how exposure to environmental levels of chemicals at levels below that required to induce toxicological or biochemical changes could induce the range of responses that constitute IEI.

Toxicant-induced loss of tolerance (TILT)

Miller proposed that drug addiction and chemical avoidance (abdiction) have many common features.[112] When chemically intolerant individuals first recognise and begin to avoid substances, they may experience headaches, fatigue, irritability, depression, myalgias and cognitive difficulties, dyspnea, dysrhythmias and gastro-intestinal problems. Subsequently, individuals in an unmasked state can identify specific triggers and avoid exposure. Further triggering of symptoms may occur through every day exposure to common chemicals, foods, drugs, food/drug combinations, for example, caffeine/alcohol. The phenomenon of TILT requires individuals to be susceptible to loss of tolerance to chemical exposure. The TILT hypothesis is an observational hypothesis but does not explain what toxicological receptor-based mechanism could result in the wide range of chemicals responsible for IEI, which also induce abdiction.

Porphyria

Evidence of porphyria has been documented in a limited number of cases of individuals with clinically diagnosed IEI.[113] It was noted that there were multiple enzyme deficiencies in many of these patients, which differed from congenital porphyria. The involvement of chemical exposure in the pathogenesis of porphyria in these individuals was unclear.

Hypoxia/hypercapnia

Ross proposed that IEI and other chronic syndromes causing fatigue, headache and other protean CNS symptoms could result from hypoxia/hypercapnia owing to disturbed breathing.[114] Some of the major symptoms of IEI, such as headache and fatigue, overlap with those of sleep apnea and could therefore result from hypoxia/hypercapnia owing to airway obstruction.[114] It is unclear how a receptor-based mechanism resulting from exposure to the wide range of chemicals responsible for IEI could lead to airway obstruction.

Evidence from studies of genotype

A limited number of studies have investigated genotype in patients with IEI. McKeown-Eyssen and colleagues reported evidence for an association between IEI and *CYP2D6* homozygous active and *NAT2* rapid but not methylene tetrahydrofolate reductase (*MTHFR*) in a case–control study of 203 clinically diagnosed female IEI patients.[115] They reported a gene dosage effect for *CYP2D6* with heterozygotes being at intermediate risk. The authors hypothesised that more rapid metabolism may confer substantially elevated risk of IEI. The biological rationale stated for investigating *CYP2D6* in part relied on evidence for slower metabolism of endogenous neurotransmitters in individuals with higher scores on anxiety and lower socialisation and the observation in some studies of a link between *CYP2D6* genotype and Parkinson's disease, Alzheimer's disease and neuroleptic-induced extrapyramidal side effects.[115] In another study, Berg and colleagues investigated genetic susceptibility factors for IEI and self-reported chemical sensitivity in a case–control study of 96 clinically diagnosed patients (80 women and 16 men) with Danish ethnicity.[116] The findings were inconsistent and no apparent association could be confirmed between chemical sensitivity and variants in the genes encoding for *CYP2D6*, *NAT2*, *MTHFR* and the cholecystokinin 2 receptor.[116]

By contrast, a case–control study of 226 individuals with either diagnosed (119 women and 14 men) or self-reported (78 women and 15 men) IEI found that the frequencies of *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5* and *UGT* gene variants were similar between the patient groups and control population.[117] There was no significant difference between the frequency of *GST* polymorphisms in the diagnosed patient group and previously published data.[117] Conversely, there was a significant decrease in erythrocyte *GST* activities and altered redox and cytokine patterns in both patient groups.[117] However, the epidemiological design of the study may be considered weak with the nonexclusion of patients suffering other inflammatory or autoimmune diseases, and selection bias may explain the observed findings.[118]

Fujimori and colleagues reported data from a case–control study of clinically diagnosed Japanese patients (41 men and 6 women) that there were no significant differences in the distribution of polymorphisms in *GSTM1*, *GSTT1*, aldehyde dehydrogenase 2 and *PON1* between patients and controls.[119] Wiesmüller and colleagues reported data from a much smaller case–control study involving patients with self-reported IEI (14 men and 45 women) and 40 controls (14 men and 26 women) that proportions of investigated polymorphisms in *5HTT*, *NAT1*, *NAT2*, *PON1*, *PON2* and *SOD2* among the patients and controls were not significantly different.[120] In contrast, Schnackenberg and colleagues reported data from a cross-sectional study (521 individuals) with self-reported chemical-related sensitivity on the distribution of genotype frequencies of *NAT2*, *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and reported that individuals being *NAT2* slow acetylators and/or harbouring a homozygous *GSTM1* and/or *GSTT1* deletion reported chemical-related hypersensitivity more frequently.[121]

In vitro studies in HEK293 cells suggest that polymorphisms of the vanilloid receptor in TRPV1 cells may be associated with changes in agonist activity of capsaicin.[122] There are no investigations of metabolism of xenobiotics in individuals with IEI. It is unclear how more rapid metabolism of xenobiotics could be related to the diverse symptoms associated with IEI. It would seem to be extremely unlikely, given the large number of trigger chemicals that metabolic activation would be a critical feature in the IEI pathogenesis. The occurrence of genotype for

cholecystokinin B receptor allele 7, which has been associated with panic disorder, was investigated in 11 IEI patients.[123] These subjects did not have a diagnosis of psychiatric or psychological disorders. The prevalence of this receptor allele was higher in IEI patients (9 of 22 alleles) compared with matched controls (2 of 22 alleles) and statistically significant ($p = 0.037$). These limited data are insufficient to reach any definite conclusion but do suggest that one possible genotype for IEI might involve a panic response. Thus, if it were established that panic response was a contributing factor to symptoms in some IEI patients, then these patients might be responsive to intervention with psychotherapy.

At present, the available evidence does not suggest a biologically relevant target that could suggest an idiosyncratic response. It is also difficult to conceive a biological rationale for selection of genes for future genotype/phenotype studies, which could account for the wide range of trigger chemicals reported for IEI. Therefore, one possible way is to undertake genome wide screening to identify possible candidate genes that might be related to the occurrence of IEI.

Discussion

It is important to evaluate the evidence regarding toxicological mechanisms for IEI in order to highlight potential exposures that might be associated with or trigger IEI or to exclude that a chemically mediated mechanism is relevant to the pathogenesis of IEI. The evidence reviewed in this article does not provide support for a receptor or idiosyncratic-mediated mechanism. It remains possible that there is a receptor-mediated trigger mechanism that could explain the onset of IEI in a number of patients. One possibility is the vanilloid receptor–mediated sensory irritancy but the available evidence reviewed here does not explain the observed wide range in trigger chemicals and the observation of generalisation, increasing response to a wider diversity of chemicals over time.

It is noted that there is a large volume of evidence that IEI can result from behavioural conditioning and epidemiological evidence that trait of absorption, anxiety and somatic attribution (tendency to attribute common somatic complaints to an illness) are associated with IEI.

The final possibility that needs explanation is whether there are toxicologically mediated trigger exposures followed by psychologically mediated development and maintenance of IEI. However, in order to study such a phenomenon, there would need to be good quality recall of trigger exposures by IEI patients, which could be difficult to achieve, or longitudinal studies of the development of IEI. A starting point would be to recruit subjects with chemical odour intolerance but without the lifestyle alteration habits of IEI patients and without the comorbid psychiatric features and then follow these individuals to see what triggers the onset of IEI. If there were convincing evidence for psychological/behavioural explanation for IEI, then this would suggest that the priority for research would be strategies for management and psychological treatment of IEI rather than investigation of possible toxicological mechanisms. Given the complexity of IEI and the remaining uncertainties regarding cause/causes, an unbiased examination of the genotypes of these patients compared with unaffected individuals might provide hypotheses for future study. It is clear from the studies to date that there are substantial questions still to be answered in order to progress understanding and treatment of IEI.

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Conflict of interest

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