differentiation that takes place in the embryo.

Nevertheless, Tsunemoto and colleagues' study adds to the body of evidence showing that some features of neuronal identity can be reproduced outside the developing brain. In doing so, it demonstrates the power of reprogramming to interrogate the function of neuron-specific genes. The authors have made their findings available in a database (see go.nature.com/2r1msxi) that will allow other researchers to use the transcription-factor codes to induce specific neuronal features. This will doubtless prove useful for studying the selective vulnerability of specific neuronal subtypes to disease.

Finally, the authors provide preliminary evidence that their transcription-factor combinations can also be used to generate neurons from human embryonic fibroblast-like cells. Following further validation, the codes might help us to decipher the origins of neuronal diversity in humans. ■

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ATMOSPHERIC SCIENCE

# Increased emissions of ozone depleters

**Chlorofluorocarbons are the main class of chemical that depleted the ozone layer in the stratosphere. Measurements reveal that emissions of these compounds are rising again, despite international rules restricting their use.** SEE LETTER P.413

MICHAELA I. HEGGLIN

Monitoring the expected decline in the atmospheric concentrations of banned compounds might seem like an unexciting research task. But on page 413, Montzka *et al.*[1] report an unexpected finding in the long-term measurements of CFC-11, one of the most potent ozone-depleting compounds: its atmospheric concentration is decreasing much more slowly than would be expected on the basis of its known sources and sinks. This points to a fresh rise in emissions — in contravention of international regulations.

CFC-11 belongs to the chlorofluorocarbon (CFC) family of compounds. CFCs are highly stable, synthetic chemicals that were used in various applications from the 1930s onwards — for example, as propellants in aerosol sprays, solvents and refrigerants. In the early 1970s, the British chemist James Lovelock and his colleagues were the first to measure the abundance of CFCs in the atmosphere and to realize that these substances were found ubiquitously in both the Northern and Southern hemispheres, despite their sources being located only in the Northern Hemisphere[2]. This finding led to the hypothesis that CFCs could be destroyed naturally only in the stratosphere, in a process that releases chlorine atoms. Each of these atoms would be able to destroy many ozone molecules in catalytically driven cycles, thus posing a threat to the ozone layer[3], which protects life on Earth from harmful ultraviolet radiation.

The discovery[4] of the 'hole' in the ozone layer over Antarctica in 1985 proved this hypothesis to be not only correct, but also much more threatening than had been imagined. It spurred research activities to understand why such severe ozone depletion was found over Antarctica alone, and led to political action to restrict the use of CFCs under the Montreal Protocol in 1987. The realization that more-severe ozone depletion would spread further across the globe if CFCs continued to be released into the atmosphere, along with technological advances that made the replacement of CFCs possible, helped governments to tighten the regulations on CFCs and ultimately ban their production through several amendments to the protocol. As a result of these actions, CFC concentrations in the atmosphere peaked in the mid-to-late 1990s and have been steadily declining ever since[5]. The Montreal Protocol has been hailed as the most successful international treaty so far that deals with a global environmental issue[6].

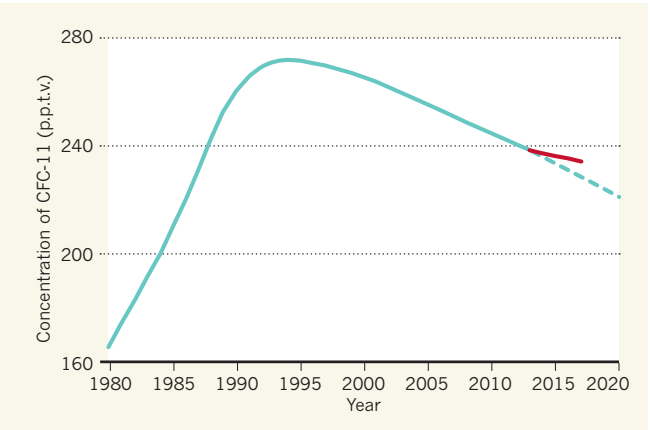


**Figure 1 | The slowing decline of an ozone-depleting compound.** Production of chlorofluorocarbons (CFCs) was banned internationally by the Montreal Protocol in 1987 because CFC emissions lead to destruction of the stratospheric ozone layer. The blue line shows the atmospheric abundance[5] of one such compound, CFC-11, in parts per trillion by volume (p.p.t.v.); the solid part indicates measurements up to 2013, and the dashed part indicates the projected abundance, assuming that no new CFC-11 is produced. Montzka *et al.*[1] report that the atmospheric abundance of CFC-11 over the past few years (red line; approximated from Fig. 1 of the paper[1]) is greater than had been projected, and so the rate of decline of CFC-11 levels is slower than expected. They conclude that CFC-11 emissions must have increased since 2012.

Because the destruction of CFCs in the stratosphere is a slow process, their removal from the atmosphere will take many decades. Today's research into stratospheric ozone focuses on whether atmospheric concentrations of ozone-depleting substances are decreasing as expected, and whether the ozone layer is on its way to recovery. Working out whether the ozone layer is recovering on the basis of ozone observations alone is particularly difficult because of confounding effects from natural variability, climate change and ozone pollution[7].

Monitoring the atmospheric concentration of ozone-depleting substances such as CFC-11 is a more direct test of the effectiveness of the Montreal Protocol. However, even for these long-lived chemicals, natural variability in the transport of air masses between the source and sink regions of the chemicals can affect the rate of the expected decline. The source regions are mostly found in

highly industrialized areas of the Northern Hemisphere, whereas CFC destruction in the stratosphere (in both hemispheres) acts as the sink. This distribution of sources and sinks leads to concentration differences between the Northern and Southern hemispheres, which get smaller over time after emissions cease. The rate of exchange of air between the stratosphere and the underlying troposphere, and between the Northern and Southern hemispheres, both have a crucial role in driving the concentrations of ozone-depleting substances.

Montzka *et al.* have made a rigorous attempt to take into account natural variability in transport between the different regions of the atmosphere to calculate how it might have generated the observed levels of CFC-11, both by using simple 'box' models and by performing 3D computational simulations using comprehensive climate models that take into account atmospheric chemistry. They conclude that variations in transport alone cannot explain the recent slowing in the rate of decline in CFCs (Fig. 1), but that new emissions must have contributed.

Further evidence in support of their hypothesis comes from their observation of an increase in the difference between mean concentrations of atmospheric CFC-11 in the Northern and Southern hemispheres over the past few years — that is, the excess of CFC-11 in the Northern Hemisphere became larger. Moreover, after 2012, they observed the emergence of a strong relationship between the atmospheric concentration of CFC-11 and the concentrations of other ozone-depleting substances emitted as a result of human activities. These multiple lines of evidence support their conclusion that changes in atmospheric dynamics, especially in the stratosphere, must be acting in concert with renewed CFC-11 emissions to produce the observed concentrations. Such a careful analysis is crucial, because any claim of renewed — and therefore illegal — emissions will have political implications.

By taking into account the flow of the atmosphere to the locations at which the CFC-11 measurements were taken, Montzka *et al.* attribute the renewed emissions to east Asia. They also estimate that these emissions amount to about 13 gigagrams of CFC-11 per year (an increase of 25%) since 2012. However, the uncertainty in the inferred magnitude of fresh emissions might be up to 50%, mainly because of the difficulty in working out how air is transported between the stratosphere and the troposphere.

One way to reduce the uncertainties in the estimates and in the probable sources of the renewed emissions would be to use a high-resolution inverse-modelling approach, such as the one that has been used[8] in regional studies to attribute sources for emissions of hydrofluorocarbons (the chemicals that replaced CFCs and that are potential greenhouse gases). However, such an approach would probably need a denser global network of CFC measurements than is currently available. Moreover, regional inverse models would have to be extended to become global, high-resolution inverse models that include a well-resolved stratosphere and inter-hemispheric transport — which is a tall order, because few such comprehensive modelling systems are currently available that come close to the needed resolution.

Montzka and colleagues' study highlights once more that environmental regulations cannot be taken for granted and must be safeguarded, and that monitoring is required to ensure compliance. Continuous observations of the environment are crucial: not only satellite measurements that yield global coverage, but also readings from measurement networks across the world that yield more-accurate *in situ* data. Taken together with models that encompass both the troposphere and the stratosphere, such data can be used to make defensible inferences about the sources of polluting chemicals. ■

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STRUCTURAL BIOLOGY

# Arresting vistas of arrestin activation

**Computational and biochemical studies have revealed the mechanisms by which arrestin proteins are activated by G-protein-coupled receptors — potentially opening up broad avenues for drug discovery.** SEE ARTICLE P.381 & LETTER P.452

BRIAN KRUMM & BRYAN L. ROTH

The largest family of drug targets in humans, and the principal therapeutic targets for at least 30% of approved medications in the United States, are the G-protein-coupled receptors[1] (GPCRs). When these transmembrane proteins detect extracellular agonist molecules, they transmit signals to the cell interior through G proteins inside the cells. The receptor is then sequentially phosphorylated to attenuate further signalling. The phosphorylated GPCR binds to an arrestin protein, and both undergo conformational changes that lead to the activation of arrestin-dependent cellular processes. Two papers in *Nature*, by Eichel *et al.*[2] and Latorraca *et al.*[3], now provide fresh insights into the mechanisms of arrestin activation and its consequences. Given the enormous potential of drugs that selectively target either G-protein or arrestin signalling, these findings might accelerate the development of safer and more-effective medications for a wide range of conditions.

Arrestins were first discovered in the visual system, where they bind to and inactivate a light-sensitive GPCR called rhodopsin[4]. They are now known to be almost universal regulators of GPCR signalling[5]. The binding of arrestin to GPCRs is enhanced by phosphorylation of the cytoplasmic tail — the carboxy terminus — of the receptors[6], and many models for arrestin binding and activation highlight the interaction of the protein with this region of the receptor.

It has been known since the 1990s that arrestins also bind at additional intracellular sites of several GPCRs, including the intracellular loops[7,8] (GPCRs have three intracellular loops that connect adjacent transmembrane regions of the receptor). In the past few years, structural[9] and biophysical studies[10] of arrestin bound to rhodopsin have clearly shown that arrestin binds to phosphorylated residues in the C terminus, as well as to a receptor core domain that includes intracellular loops 2 (IL2) and 3 (IL3). How these interactions lead to activation of arrestin and subsequent signalling has been obscure.

Latorraca and colleagues now cast light on this issue. The authors began by performing extensive computational simulations of the molecular dynamics of arrestin, both alone and during its interaction with various regions of rhodopsin. Their results indicate that 'active' arrestin fluctuates between active and inactive states, and that the receptor core domain and the phosphorylated tail can individually stabilize arrestin's active state. Moreover, the active