The effects of repeated brain MRI on chromosomal damage

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- Magnetic resonance imaging (MRI) is currently considered a safe imaging technique because, unlike computed tomography, **MRI does not expose patients to ionising radiation.** However, conflicting literature reports possible genotoxic effects of MRI. We herein examine the chromosomal effects of repeated MRI scans by performing a longitudinal follow-up of chromosomal integrity in volunteers.
- Methods
- This ethically approved study was performed on 13 healthy volunteers (mean age 33 years) exposed to up to 26 3-T MRI sessions. The characterisation of chromosome damage in peripheral blood lymphocytes was performed using the gold-standard biodosimetry technique augmented with telomere and centromere staining.
- Results
- Cytogenetic analysis showed no detectable effect after a single MRI scan. However, repeated MRI sessions (from 10 to 20 scans) were associated with a small but significant increase in chromosomal breaks with the accumulation of cells with chromosomal terminal deletions with a coefficient of 9.5% (95% confidence interval 6.5–12.5%) per MRI ($p < 0.001$). Additional exposure did not result in any further increase. This plateauing of damage suggests lymphocyte turnover. Additionally, there was no significant induction of dicentric chromosomes, in contrast to what is observed following exposure to ionising radiation.
- Conclusions
- **Our study showed that MRI can affect chromosomal integrity.** However, the amount of damage per cell might be so low that no chromosomal rearrangement by fusion of two deoxyribonucleic breaks is induced, unlike that seen after exposure to computed tomography. This study confirms that MRI is a safe imaging technique.
- Key points
- A longitudinal follow-up of genotoxicity was conducted on volunteers receiving repetitive (up to 26) 3-T magnetic resonance imaging (MRI) brain scans.
- One single MRI session of 90 min had no impact on chromosomal integrity.
- Repetitive MRI scans ($n = 20$) over a 2-year period showed a small increase in chromosome breaks that reached a plateau thereafter. These breaks concerned only chromosome terminal deletions but not dicentrics (which can be observed after computed tomography exposure) and are considered hallmarks of irradiation damage.
- MRI remains one of the safest imaging techniques.

Suppressor Mutations

- Suppose that point mutations lead to structural changes in one protein (A) that disrupt its ability to associate with another protein (B) involved in the same cellular process.

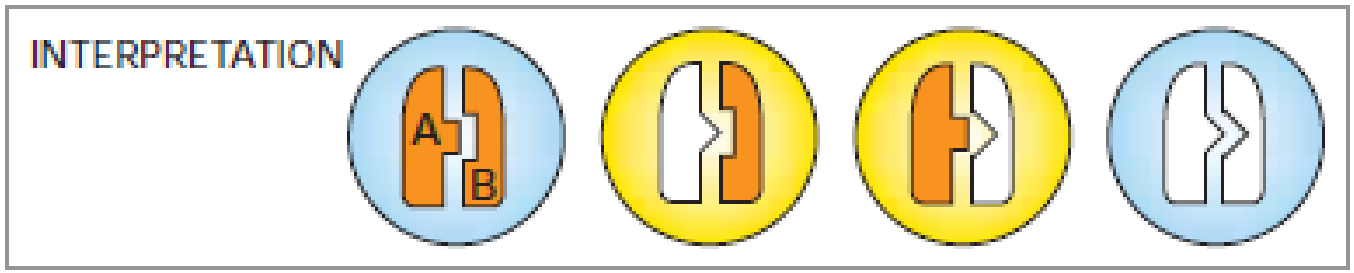
- Similarly, mutations in protein B lead to small structural changes that inhibit its ability to interact with protein A.
- Further, that the normal functioning of proteins A and B depends on their interacting.

- In theory, a specific structural change in protein A might be suppressed by compensatory changes in protein B, allowing the mutant proteins to interact.

In the rare cases in which such suppressor mutations occur**, strains carrying both mutant alleles would be normal**, whereas **strains carrying only one or the other mutant allele would have a mutant phenotype**

(a) Suppression

Genotype	*AB*	*aB*	*Ab*	*ab*
Phenotype	Wild type	Mutant	Mutant	Suppressed mutant

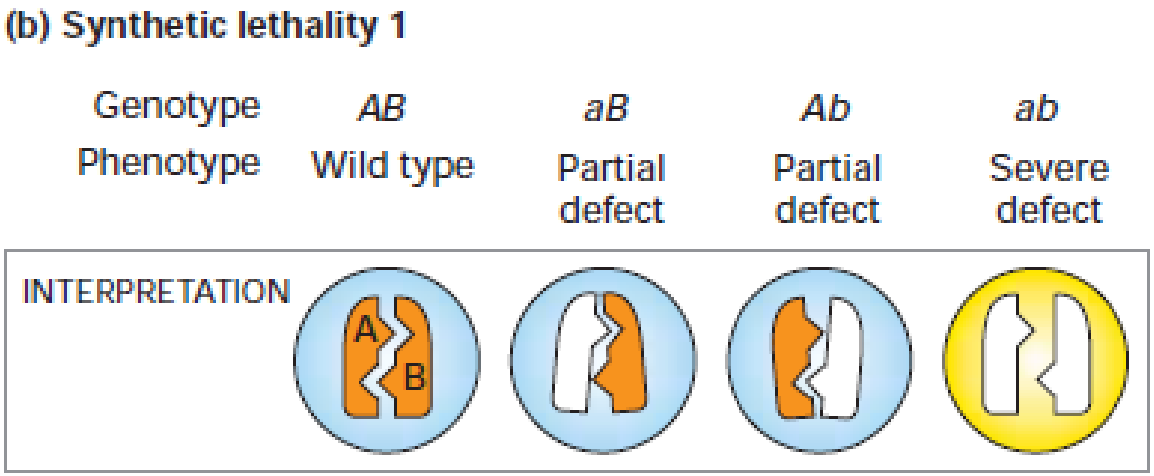


Synthetic Lethal Mutations

Another phenomenon, called *synthetic lethality, produces a phenotypic effect opposite to* that of suppression. In this case, the deleterious effect of one mutation is greatly exacerbated (rather than suppressed) by a second mutation in the same or a related gene.

In this example, a heterodimeric protein is partially, but not completely, inactivated by mutations in either one of the nonidentical subunits.

However, in double mutants carrying specific mutations in the genes encoding both subunits, little interaction between subunits occurs, resulting in severe phenotypic effects.



Mutagens act through at least three different mechanisms.

They can *replace a base in the DNA, alter a base* so that it specifically mispairs with another base, or *damage* a base so that it can no longer pair with any base under normal conditions.

BASE REPLACEMENT Some chemical compounds are sufficiently similar to the normal nitrogen bases of DNA that they are occasionally incorporated into DNA in place of normal bases; such compounds are called **base analogs.**

Many of these analogs have pairing properties unlike those of the normal bases; thus they can produce mutations by causing incorrect nucleotides to be inserted in the course of replication.

Genetic studies have shown that **2-AP, like 5-BU**, is highly specific for transitions.

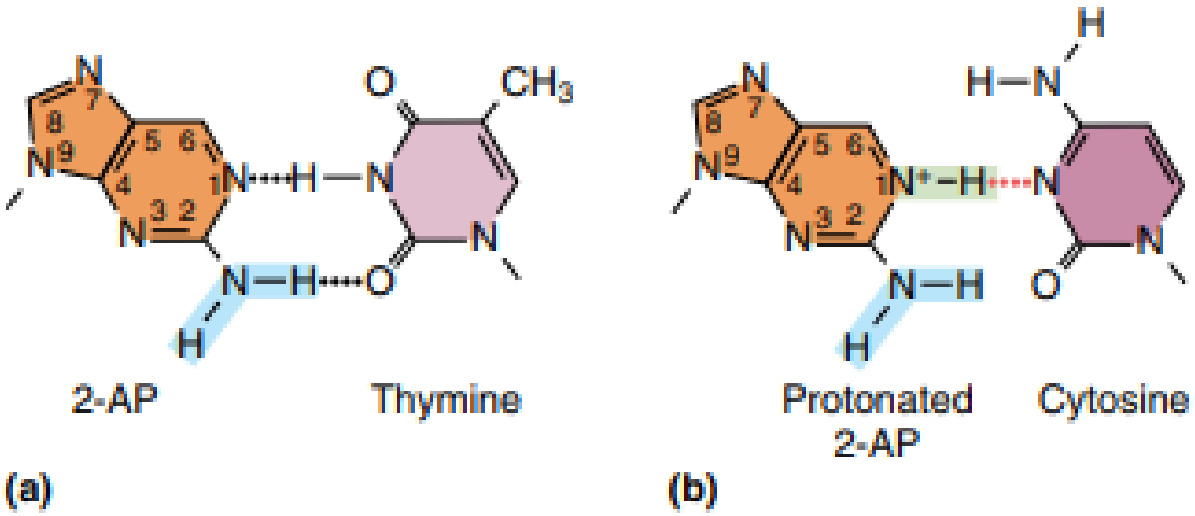


Figure 14-8 Alternative pairings for 2-aminopurine (2-AP). This analog of adenine can pair with cytosine in its protonated state (b).

BASE ALTERATION Some mutagens are not incorporated into the DNA but instead alter a base, causing specific mispairing.

Certain alkylating agents commonly used as mutagens, such as **ethylmethanesulfonate (EMS) and nitrosoguanidine (NG),** operate by this pathway.

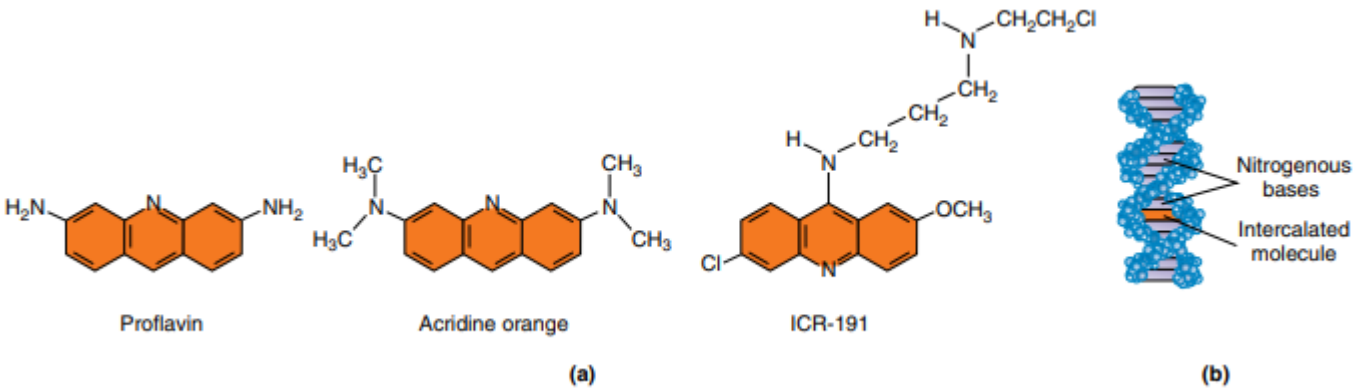
Such agents add alkyl groups (an ethyl group in the case of EMS and a methyl group in the case of NG) to many positions on all four bases. However, a mutation is most likely to occur when the alkyl group is added to the oxygen at position 6 of guanine to create an *O-6*-alkylguanine.

This alkylation leads to direct mispairing with thymine, and results in G · C : A · T transitions in the next round of replication.

Alkylating agents can also modify the bases of incoming nucleotides in the course of DNA synthesis.

The **intercalating agents are another important class** of DNA modifiers. This group of compounds includes **proflavin, acridine orange, and a class of chemicals** termed **ICR compounds.**

These agents are flat planar molecules that mimic base pairs and are able to slip themselves in *(intercalate) between the* stacked nitrogen bases at the core of the DNA double helix. In this intercalated position, an agent can cause single-nucleotide-pair insertions or deletions.



BASE DAMAGE

- **A large number of mutagens *damage*** one or more bases; so no specific base pairing is possible.
- The result is a replication block, because DNA polymerase cannot continue DNA synthesis past such a damaged template base.
- In both prokaryotes and eukaryotes, such replication blocks can be *bypassed by inserting nonspecific* bases.

- In *E. coli, this process requires the activation* of the **SOS system.**

- The name *SOS comes from the idea that* this system is induced as an emergency response to prevent cell death in the presence of significant DNA damage.

- As such, SOS induction is a mechanism of last resort, a form of damage tolerance that allows the cell to trade death for a certain level of mutagenesis.

Aflatoxin B1 (AFB1) is a powerful carcinogen originally isolated from peanuts infected with a fungus. Aflatoxin attaches to guanine at the N-7 position. The formation of this addition product leads to the breakage of the bond between the base and the sugar, thereby liberating the base and resulting in an **apurinic site.**

Studies of apurinic sites generated in vitro have demonstrated that the SOS bypass of these sites often leads to the insertion of an adenine residue across from an apurinic site. Thus, agents that cause depurination at guanine residues should tend to induce G · C : T · A transversions.

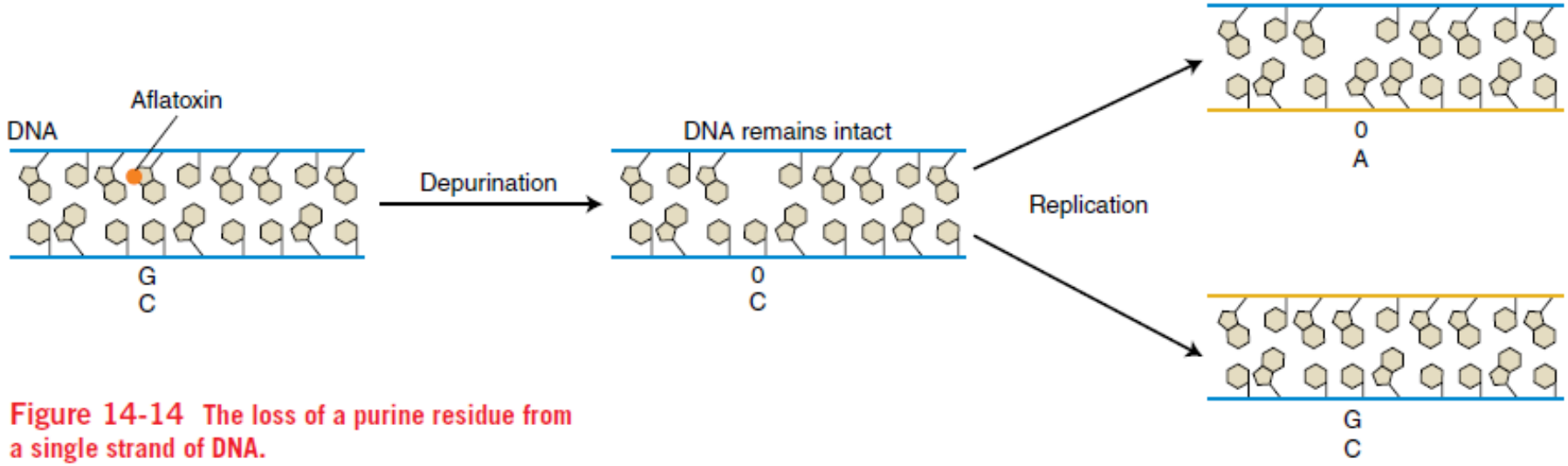


Figure 14-14 The loss of a purine residue from a single strand of DNA.

Bacteria are fast-dividing and take up little space, so they are very convenient to use as genetic model organisms.

They can be cultured in a liquid medium, or on a solid surface such as an agar gel, so long as basic nutrients are supplied.

Each bacterial cell divides from 1 : 2 : 4 : 8 : 16, and so, on until the nutrients are exhausted or until toxic waste products accumulate to levels that halt the population growth.

Bacterial mutants are also convenient. Wild-type bacteria are **prototrophic.** This means they can grow and divide on minimal medium—a substrate containing only inorganic salts, a carbon source for energy, and water.

From a prototrophic culture, **auxotrophic mutants** can be obtained: these are cells that will not grow unless the medium contains one or more specific cellular building blocks such as adenine, threonine or biotin.

A small amount of a liquid culture can be pipetted onto a petri plate containing solid agar medium and spread evenly on the surface with a sterile spreader, in a process called **plating**.

The cells divide, but because they cannot travel far on the surface of the gel, all the cells remain together in a clump. When this mass reaches more than 10^7 cells, it becomes visible to the naked eye as a **colony.**

Each distinct colony on the plate will be derived from a single original cell. Members of a colony that share a single genetic ancestor are known as a cell **clone.**

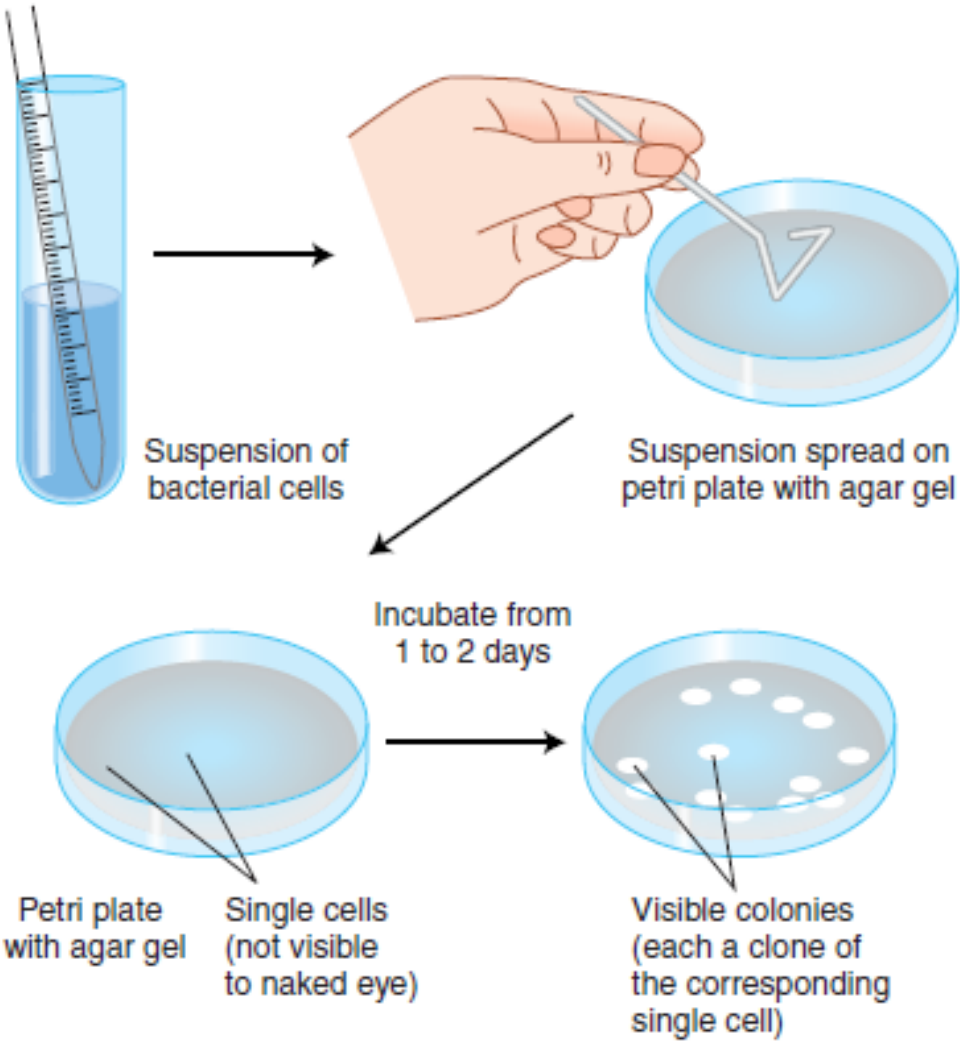


Figure 5-2 Methods of growing bacteria in the laboratory. Bacteria can be grown in liquid media containing nutrients. A small number of bacteria from liquid suspension can also be spread on agar medium containing nutrients. Each cell will give rise to a colony. All cells in a colony have the same genotype and phenotype.

Spontaneous mutation

One of the first questions asked by geneticists was whether spontaneous mutations are induced in response to external stimuli, or whether variants are present at a low frequency in most populations.

An ideal experimental system to address this important question was the analysis of mutations in bacteria that confer resistance to specific environmental agents not normally tolerated by wild types.

Luria and Delbrück fluctuation test

It was known at the time that if *E. coli bacteria are spread on a plate of nutrient* medium in the presence of phage T1, the phage soon infect and kill the bacteria.

However, rarely but regularly, colonies were seen that were resistant to phage attack; these colonies were stable and so appeared to be genuine mutants.

However, it was not known whether these mutants were produced spontaneously but randomly in time or whether the presence of the phage induced a physiological change that caused resistance.