COMMENTARY

MAPK activation by radio waves

J. Simon C. ARTHUR¹

MRC Protein Phosphorylation Unit, School of Life Sciences, University of Dundee, Dundee, DD4 5EH, U.K.

In this issue of the *Biochemical Journal*, Friedman et al. report the findings of a study to look at the potential of mobile phones to activate intracellular signalling cascades. They found that radio waves corresponding to the frequency commonly used by mobile phones are able to activate ERK1/2 (extracellular-signal-regulated kinases 1 and 2). This effect was observed even at intensities lower than those emitted by mobile phones that are unable to cause any measurable heating effects. This study provides evidence that

radio waves induce ERK1/2 activation downstream of the EGF (epidermal growth factor) receptor, which is in turn activated by the release of reactive oxygen species.

Key words: extracellular-signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), mobile phone, reactive oxygen species, ultra-high frequency radio wave (UHF radio wave).

Over the last 10 to 15 years, there has been a large increase in the use of mobile phones, and more recently in wireless computer networks. These networks transmit information using either the UHF (ultra-high frequency; 300 MHz to 3 GHz) or SHF (super-high frequency; 3 GHz to 30 GHz) sections of the electromagnetic spectrum, and this has raised controversial questions about the safety of this technology, particularly with regard to its potential to induce cancer. If UHF waves are able to induce pathology, it would be predicted that they would be able to directly affect biological systems. The mechanism by which they would do this is, however, unclear. High intensities of UHF radio waves can cause measurable heating effects in biological tissues; however, this requires a much higher intensity of UHF waves than is used by wireless technology. The ability of other electromagnetic waves, such as X-rays and UV light, to cause DNA damage and promote tumorigenesis has been well documented. Both X-rays and UV light, however, have much higher frequencies than UHF waves, and as a result carry considerably more energy. In the case of X-rays and UV radiation, this energy is sufficient to break chemical bonds in DNA; however, it has been calculated that radio waves carry insufficient energy to do this [1,2]. Consistent with this, radio waves have been reported to be unable to directly cause DNA damage, and studies on the effect of radio waves on tumour formation in rodents have failed to show any consistent association between exposure to radio waves and tumours [1,2].

Is it possible then that UHF waves could have effects on cells at levels that do not induce thermal effects? In this issue of the *Biochemical Journal*, Friedman et al. [3] show that UHF radio waves are able to induce activation of the Raf–MEK1/2 [MAPK (mitogen-activated protein kinase)/ERK (extracellular-signal-regulated kinase) kinases 1/2]–ERK1/2 signalling cascade. The ERK1/2 cascade is the archetypal member of the MAPK cascades, a group that also includes the p38 and JNK (c-Jun N-terminal kinase) cascades. The ERK1/2 cascade has been studied extensively, and it is known to be activated by a variety of stimuli, including growth factors [such as EGF (epidermal growth factor)], mitogens and oxidative stress. ERK1/2 is involved in the regulation of many cellular processes, including proliferation, survival and differentiation, whereas mutations that cause constitutive activation of this cascade are implicated in

several cancers [4,5]. Friedman et al. [3] found that irradiation of either Rat1 or HeLa cells using radio waves in the frequency range 80–950 MHz was able to induce a transient activation of ERK1/2 that peaked after 10 min of stimulation. The intensity of UHF radiation used in these experiments was lower than that emitted by most mobile phones, and was found not to affect the temperature of the media. In contrast with the activation of ERK1/2, no activation of p38 or JNK activation was observed after short-term irradiation, although in line with some previous reports some p38 and JNK was observed following an irradiation of several hours [6,7].

As expected, the activation of ERK1/2 by UHF radio waves was inhibited by PD098059, an inhibitor of the upstream MEK1/2 kinases. The authors showed further that the activation of ERK1/2 was blocked by AG1478, an inhibitor of the EGF receptor. EGF is well known for its ability to activate ERK1/2, and it is likely that the molecular details of ERK1/2 activation downstream of the EGF receptor in response to UHF radiation are similar to that in response to EGF. This, however, raises the question of how UHF radiation is able to activate the EGF receptor. The authors suggest that this is due to an ability of UHF radio waves to induce reactive oxygen species, since ERK activation was blocked by the reactive oxygen scavenger NAC (*N*-acetylcysteine). The authors propose that reactive oxygen species are able to activate matrix metalloproteinases. These are then able to cleave proHb–EGF (pro-heparin-binding EGF) expressed on the cell surface. This then releases Hb–EGF into the media, from where it is then able to activate the EGF receptor. As observed by the authors, components of this mechanism have been shown to be involved in the activation of ERK1/2 by hydrogen peroxide or G-protein-coupled receptors. The activation of MAPKs by ionizing radiation has also been suggested to occur through a similar mechanism [8]. This is, however, the first time this pathway has been shown to act downstream of UHF radio waves. The authors suggest further that the molecular target of UHF radio waves may be a membrane-bound NADH oxidase, the activation of which would promote the generation of reactive oxygen species. Further work, however, is needed to fully characterize the details of this process.

Given that UHF waves can induce MAPK activation, what implication does this have for the safety of mobile phone use?

¹ email j.s.c.arthur@dundee.ac.uk

There have been many recent studies to look at the potential link between mobile phones or radio transmitters and cancer. To date, these have not been able to show conclusively a link between radio waves and cancer [1,2]. It should be noted that these studies have many technical problems, of which one of the most significant is that they have all had to rely on estimates of exposure to electromagnetic radiation. This is compounded by the fact that exposure is not directly proportional to distance from a transmitter, as it is also influenced by geographical features and interference between different radio signals. Concern has also been raised with respect to mobile phone use, as these transmit UHF radio waves next to the user's head, which would therefore increase the potential for exposure. Again, it has been difficult to study this problem, in part because head and neck cancers are relatively infrequent. As a result, most studies carried out have been case control studies rather than population studies. Overall, there is little evidence to suggest that short-term mobile phone use carries a significant increased risk of cancer [1,2]. More recently some, but not all, longer-term studies that have looked at 10 or more years of mobile phone use have suggested that there may be a slight increase in the risk of head and neck cancers; however, these findings are still controversial (for example, see [9]). Is the ability of UHF radio waves to activate ERK1/2 signalling likely to have an impact on this? ERK1/2 has been strongly implicated in carcinogenesis, and inhibitors of the ERK1/2 pathway have attracted considerable interest as anticancer drugs. The role of ERK1/2 in cancer, however, usually occurs downstream of an activating somatic mutation of one of the upstream activators of ERK1/2, such as Raf. This results in a strong constitutive activation of the ERK1/2 pathway, leading to cellular transformation. Transient and reversible activation of the ERK1/2 pathway, such as would be induced by UHF radio waves, is unlikely to be oncogenic. Indeed, transient activation of ERK1/2 occurs frequently in cells in response to a huge variety of signals, and is an essential component of many aspects of cellular physiology. Possibly of more concern is the potential mechanism of action of UHF radio waves. Reactive oxygen species can activate several intracellular signalling pathways, which may in some cases actually serve to protect cells from the harmful effects of reactive oxygen species. Independently of this, reactive oxygen species also have the potential to cause DNA damage. This can result in somatic mutations, and these can potentially be oncogenic [10]. It could be argued that long-term exposure to reactive oxygen species induced by radio waves would eventually lead to an increased risk of cancer, and that this effect has not been seen in rodents owing to the short lifespan of these animals. Against this, however, the ability of UHF to induce the reactive oxygen species has not been studied extensively, and whereas

some reports confirm this ability [11], others find no evidence for it [12,13]. In addition, reactive oxygen species are commonly induced in the body as a result of many processes, and organisms have many ways of limiting their potential damage. If UHF radio waves are able to induce reactive oxygen species in cells, it would then be necessary to quantify this and set it in the context of the total cellular exposure to reactive oxygen species.

In summary, Friedman et al. [3] have been able to add UHF radio waves to the stimuli capable of activating ERK1/2, and have elucidated the mechanism by which this occurs. Further work will be required to assess the potential pathological role of these findings.

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