**Cellular Redox Environment and its Influence on Redox Signalling Molecules**

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Short title: Influence of redox on signalling

**Abstract**

The redox potential of a cell’s internal environment is well recognised as important for controlling cellular activities. Both animal and plant cells generate and are exposed to a range of reactive molecules involved in cell signalling, including reactive oxygen species and reactive nitrogen species, such as hydrogen peroxide and nitric oxide. Redox active molecules exist in different oxidation states, with the ratio of the states being able to be determined using the Nernst equation. Therefore influence of redox environments of cells on the likelihood of the persistence of a particular redox state of a molecule can be estimated, and this might have a profound effect on whether molecules can act as signals. Although the cellular redox may have little influence on some molecules, for others there may be a significant impact from the redox environment. Furthermore, cellular redox environments fluctuate and as they become more oxidising some signalling molecules may become more persistent while the moderating effect of others may be lessened. Such influence of redox environment needs to be taken into account if the role of such molecules in cell signalling is to be understood.

**Introduction**

The redox environment inside cells has been the subject of considerable discussion over many years [1-3]. It is important to understand as it is used for the maintenance of reduced compounds and for cell signalling. The intracellular reduction potential has been estimated to be relatively reducing [2] (normally lower than -200mV relative to a standard hydrogen electrode), therefore giving an ideal environment for the production and maintenance of reduced co-factors such as NADH and NADPH. However, the actual concentrations of such co-factors in cells will also be influenced by their binding to other cellular components [1, 6]. It is important to also understand that the redox environment of cells is not fixed, but has a dynamic nature. Schafer and Buettner [2] estimated that the redox environment may become significantly more oxidising, changing by as much as 70mV as cells move from a proliferative state to one of apoptosis. Such changes can have profound effects on cellular components such as proteins, and therefore redox signalling is now recognised as a major influence in the control of cellular function [7].

One of the most significant influences on the redox environment is both the amount and reduction state of the tri-peptide glutathione [2]. Intracellular concentrations may be greater than ten millimolar. Its influence on the redox is determined by its mid-point potential [8], but also by its overall concentration because the reaction relates to a squared ratio in the Nernst Equation [2]. Cells can therefore manipulate their intracellular redox by the generation [9] or loss of glutathione [10] as well as the ratio of the oxidised to reduced states [2]. Therefore, glutathione can be measured as an estimate of the intracellular redox state [11] and its influence has been linked to health and disease [12] especially as it can also alter protein function through glutathionylation [13].

The presence, or accumulation, of other redox molecules also influences intracellular redox states, including reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS encompasses superoxide anions, hydrogen peroxide (H2O2) and the hydroxyl radical while RNS includes nitric oxide and peroxynitrite. Both ROS and RNS are known to be major signalling molecules in both plants and animals [4-5] and can cause post-translational modifications of proteins and so control cellular function: oxidation and *S*-nitrosylation respectively [14].

Other signalling molecules here include hydrogen sulfide (H2S) [15] and hydrogen gas (H2) [16]. H2S can lead to *S*-sulfhydration [17], altering protein function, perhaps in competition with other redox active molecules [15], while H2 can influence cellular redox by manipulating antioxidant levels [18].

The present dogma is that ROS and other redox molecules influence the redox environment and that this leads to the process of oxidative stress, leading to cellular damage [19]. To some extent this is probably true, with considerations of compartmentalization being taken into account. However, it is argued here that the opposite is also true, that the redox environment of the cell will be a major influence on whether redox signalling molecules persist in the cell and whether they are able to have effects often assigned to them.

**Maintenance and influence of redox environments**

The redox environment will be dictated by the major redox-capable components of the cellular location; the cytoplasm is commonly studied. It is considered that intracellular glutathione is a good indicator of redox poise [2], with values being derived using the Nernst equation (Equation 1: bearing in mind the squared ratio needed for the GSSG/2GSH couple).

Equation 1: The Nernst Equation (redox equation) assuming an intracellular pH of 7.4.

Eh = Em(pH7.4) + RT x 2.303Log [oxidised]

nF [reduced]

where: Eh is the redox potential; Em(pH7.4) is the midpoint potential of redox couple at pH7.4; R is the Gas Constant; T is the temperature in Kelvin; F is the Faraday Constant; n is the number of electrons used in oxidation/reduction.

However, the redox environment will also be determined by the presence of other abundant low-molecular weight (LMW) thiols (Table 1) [20], including cysteine (Cys), cysteinyl-glycine (Cys-Gly) and -glutamyl-cysteine (-Glu-Cys). It was found that in non-aged seeds non-GSH thiols contributed to approximately 15% of the redox which involved thiol-disulfide reactions (Ethiol-disulphide), while this increased to approximately 25% in 10 week old seeds. A shift in this redox couple was correlated to the loss of seed viability, showing that there was a real biological effect [20]. Methods for measuring the couples for glutathione (GSSG/2GSH), cysteine/cystine (cys/cySS), thioredoxins (TRX(red)/TRX(ox) and the oxidation states of proteins have been described [3] while Schafer and Buettner [2] suggested that the equation to calculate the redox environment should include all redox influencing species (Equation 2).

Equation 2:

n (couple)

Redox environment = Σ Ei x [reduced species]i

i-1

Where Ei is the half-cell reduction potential of the redox couple of interest [2].

Given that the GSSG/2GSH couple alone could be millimolar [2, 21] these thiol couples (Table 1) will be the overriding factors keeping the intracellular redox environment stable. Given also that 25% of the environment could be influenced by other LMW thiols [20] the total thiol concentration maintaining redox poise in cells is significant. To influence this the concentrations of ROS and RNS added to make an appreciable difference would have to be considerable.

The most studied ROS is H2O2, with effects reported at low levels, such as 10 µM in work on *C. elegans* [21]*,* and 1-20 µM in a study of synaptic plasticity [22]. Although some organisms such as Streptococcus and Enterococcus bacteria can produce H2O2 to higher levels, such as 2mM [23], very high levels in human tissues would be considered to be 600 µM, as in eye aqueous humour [21]. The influence on redox environment through Equation 2 must be limited if H2O2 is considerably lower than the 10mM of glutathione. It is hypothesised here that the influence will be the other way around, that is, the redox environment will have a major impact on the [oxidised]/[reduced] ratio of the signalling molecule. There is a caveat. Intracellular redox environment studies usually measure the overall redox state, but as with other signals, redox components will be compartmentalized [24] and actual levels of LMW thiols, ROS and RNS may be different to those measured. Having said that, there have been reports of intracellular redox values (Table 2) with an average value of approximately -242 mV. Taking these data, using published data for the mid-point potentials for redox couples which could be important for cell signalling and using the Nernst Equation (Equation 1) estimates of the [oxidised]/[reduced] value for a range of redox couples can be obtained (Table 3). Furthermore, as a cell moves from a proliferative state to one of apoptosis [2] how a change of redox environment may influence the [oxidised]/[reduced] of signalling couples can be calculated (Table 3).

For many redox couples there is no tangible influence of the redox environment on the likely biological activity of those signalling molecules. At -242 mV the O2/H2O2 couple will vastly favour the presence of H2O2, enabling H2O2 to act as a cellular signal. A change of intracellular redox of approximately 70mV will make little difference to this. Many of the redox couples listed (Table 3) have mid-point potentials significantly more positive than the redox environment, so changes of ~70 mV makes no difference; there is little effect on important couples such as RO·/ROH and RS·/RSH for example, although local peptide environments may influence here. There will be little influence on some non-protein couples, such as NO+/NO·, favouring NO· at all cellular redox potentials. As NO+ and NO· will react in different ways [25], and NO· being the species associated with signalling, this is important.

Cellular redox does influence redox ratios however. For the O2·-/H2O2 couple H2O2 is favoured, which would aid signalling where a molecule has to persist and move to have influence. However, for the O2·-/H2Oand H2O2/H2O couples cellular redox would favour the conversion to H2O: not good for signalling. The presence of the signalling species is also not favoured for the 2H+/H2 couple: the proton to gas ratio being ~1000; the gas being important for signalling [16]. For the ONOO-/NO2 couple peroxynitrite may not be persistent in cells, although peroxynitrite is relatively stable and known to have biological effects [26].

The reduction of cytochrome *c* is favoured. The oxidation of cytochrome *c*, as affected by ROS, may have a role in the activation of cell death programmes [27]. It may be expected, therefore, that the oxidation of cytochrome *c* and its protein interactions would have to be compartmentalised to avoid immediate re-reduction.

Along with the influence of average cellular redox it can be determined if changes in redox have an influence, that is, oxidation by approximately 70 mV [2]. The O2/O2·- couple sees a significant lowering of O2·- concentrations, so diminishing the bio-availability of O2·- and lowering the possible H2O2 concentrations resulting from dismutation. For the H+/H2 couple the preference for the gaseous (signalling) form would be lowered, whereas for the NO·/NO- couple the preference moves to the NO· (signalling) form. The RSNO/RSH couple will favour the RSNO form, helping to drive, or prolong, RSNO signalling. The S/H2S couple will lower the H2S concentration: H2S may keep other redox signalling under control [15] so the influence of H2S goes down, the influence of RSNO goes up, so allowing redox signalling to continue, or even increase.

**Conclusions and perspectives**

The redox environment of the cell is extremely important and is maintained at a relatively reducing potential by a range of small thiol compounds. This reduction potential will have little influence on many biological-relevant redox couples but for some it may be important. The presence of H2O2 and NO· may be favoured, both which are important for signalling, while the presence of H2 may be low. However, the redox of the cell is not static and as it becomes oxidising this may have an influence on redox couples: O2·- presence may be lowered, as may that of H2S while NO· may be favoured. Therefore, the influence of intracellular redox on redox-sensitive signalling molecules needs to be considered.

Future work needs to fully understand the redox environment at a local level to get a complete understanding of the effect on redox couples in cells. As with many signalling processes compartmentalisation is important to consider and will give a better understanding of the prevalence of the oxidation state of important signalling molecules in cells.

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|  |  |  |  |
| --- | --- | --- | --- |
| Redox couple | Notes | Mid-point potential (mV) | Reference(s) |
| GSH/GSSG | *E0’ (pH=7.0)* | -240 | [8, 20] |
| GSH/GSSG | *E pH=7.4* | -264 | [2] |
| GSH/GSSG | *E pH=8* | -299 | [2] |
| Cys-bis-Gly/2 Cys Gly | *E0’* | -226 | [20, 28] |
| Cysteine/2 Cys | *E0’* | -226 | [20, 28] |

**Table 1:**

**Redox couples which are instrumental in controlling the redox environment.**

|  |  |  |
| --- | --- | --- |
| Cell type (proliferating) | Eh pH7.4 (mV) | Reference(s) |
| Normal fibroblasts | -247 | [29] |
| Fibrosarcoma | -238 | [29] |
| Murine hybridoma | -235 | [30, 31] |
| Human lymphocytes | -237 | [32] |
| Jurkat | -240 | [32] |
| Murine hybridoma | -257 | [33] |
|  |  |  |
| *Average* | *-242* |  |
|  |  |  |
| Cells proliferating | -242 | [2] |
| Cells differentiating | -200 | [2] |
| Cells under apoptosis | -170 | [2] |
| Liver cytosol | -390 | [6] |

**Table 2: Redox potentials of various cell environments [2].**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Redox couple  Eo’  (mV) | e-  (n=) | At -390 mV (liver cytosol) # | At -242 mV (proliferating)\*\* | At -200 mV (differentiating)  \*\*\* | At -170 mV (apoptotic)\*\*\* | Comments/ Reference(s) for mid-point potentials |
| NAD+/NADH | | | | | | |
| -320## | 2 | 4.3x10-3 | 431.6 | 1.1x104 | 1.1x105 | Probably ~1:100. Bound to cytosolic binding sites ### |
| O2/O2·- | | | | | | |
| -160 | 1 | 1.3x10-4 | 4.1x10-2 | 0.21 | 0.68 | [34] |
| O2/H2O2 | | | | | | |
| +300 | 2 | 4.9x10-24 | 4.9x10-19 | 1.3x10-17 | 1.3x10-16 | [34] |
| O2·-/H2O2 | | | | | | |
| +940 | 1 | 3.4x10-23 | 1.1x10-20 | 5.5x10-20 | 1.8x10-19 | [34] |
| O2·-/H2O | | | | | | |
| +1200 | 3 | 1.9x10-81 | 6.3x10-74 | 8.6x10-72 | 2.9x10-70 | Quoted as [O2·-]/[H2O]2  [34] |
| H2O2/H2O | | | | | | |
| +1320 | 2 | 9.1x10-49 | 9.1x10-44 | 2.4x10-42 | 2.5x10-41 | Quoted as [H2O2]/[H2O]2  [34] |
| Dehydroascorbic acid/ascorbic acid | | | | | | |
| +80 | 2 | 1.3x10-16 | 1.3x10-11 | 3.5x10-10 | 3.6x10-9 | [35]  [36] |
| Cytochrome *c* (ferric/ferrous) | | | | | | |
| +220 | 1 | 5.0x10-11 | 1.6x10-8 | 8.0x10-08 | 2.6x10-7 | [35] |
| 2H+/H2 | | | | | | |
| -420 (30oC) | 2 | 10.3 | 1.0x106 | 2.7x107 | 2.8x108 | Values quoted as [H+]2/H2  [35,37] |
| -413 (25oC) | 2 | 6.0 | 6.0x105 | 1.6x107 | 1.6x108 | [38] |
| OH·/H2O | | | | | | |
| +2310 | 1 | 2.5x10-46 | 7.8x10-44 | 4.0x10-43 | 1.3x10-42 | [39] |
| H2O2/OH- (H2O) | | | | | | |
| +320 | 1 | 1.0x10-12 | 3.2x10-10 | 1.6x10-9 | 5.3x10-9 | [39] |
| NH3+/NH3 | | | | | | |
| +2130 | 1 | 2.7x10-43 | 8.6x10-41 | 4.4x10-40 | 1.4x10-39 | [40] |
| NO+/NO· | | | | | | |
| +1210 | 1 | 9.4x10-28 | 3.0-x10-25 | 1.5x10-24 | 4.9x10-24 | [39] |
| NO·/NO- (singlet) | | | | | | |
| -350 | 1 | 0.21 | 66.7 | 341.8 | 1097.8 | [39] |
| NO·/NO- (triplet) | | | | | | |
| +390 | 1 | 6.7x10-14 | 2.1x10-11 | 1.0x10-10 | 3.5x10-10 | 39 |
| 2NO-/N2O2- | | | | | | |
| +650 | 1 | 2.7x10-18 | 8.6x10-16 | 4.4x10-15 | 1.4x10-14 | Value quoted as [NO-]2/[N2O2-]  [39] |
| 1O2/O2·- | | | | | | |
| +830 | 1 | 2.5x10-21 | 7.8x10-19 | 4.0x10-18 | 1.3x10-17 | [39] |
| ONOO-/NO2 | | | | | | |
| +1400 | 1 | 5.8x10-31 | 1.8x10-28 | 9.4x10-28 | 3.0x10-27 | [39] |
| NO2/NO2- | | | | | | |
| +990 | 1 | 4.9x10-24 | 1.5x10-21 | 7.9x10-21 | 2.5x10-20 | [39] |
| +1040 | 1 | 7.0x10-25 | 2.2x10-22 | 1.1x10-21 | 3.6x10-21 | [41] |
| RO·/ROH | | | | | | |
| +1600 | 1 | 2.4x10-34 | 7.7x10-32 | 3.9x10-31 | 1.3x10-30 | [39] |
| RS·/RSH | | | | | | |
| +900 | 1 | 1.6x10-22 | 5.1x10-20 | 2.6x10-19 | 8.4x10-19 | [39] |
| RSNO/RSH, NO· | | | | | | |
| -400 | 1 | 1.4 | 466.5 | 2389.9 | 7676.0 | [39] |
| S/H2S | | | | | | |
| -230 | 2 | 3.9 | 0.4 | 10.3 | 106.4 | [42] |

**Table 3:**

**Theoretical values of various redox ratios at proposed redox environments.**

\* [2, 6, 43, 44]; \*\* Table 1; \*\*\* [2]; # [6, 43, 44]; ## [37]; ### [1,6].