MEDICAL CARBONS - NEED FOR MESOPORES

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Introduction

At present medical activated carbons (AC) are used as oral adsorbents and for haemoperfusion mostly in acute poisoning with small molecular weight toxins. Respectively, the efforts to make an efficient medical activated carbon are aimed at developing its microporous structure. Potential for therapeutic use of activated carbon with larger pores – mesopores is almost completely overlooked and ignored. The main reasons for this are two-fold. It is a common perception that oral administration of activated carbon is efficient only within first 1-2 hours after acute poisoning, and acute poisoning is usually caused by small molecules of drugs, pesticides and other chemicals. In haemoperfusion mostly coated activated carbons are used. The coating is usually made of a more biocompatible cellulose membrane. Although AC coating resolved the problem of its poor biocompatibility, it created another one, which restricted use of adsorption therapy in comparison with alternative blood purification techniques such as dialysis or filtration. A 0.5-5 μm thick semi-permeable coating (i) slows down the external diffusion to the adsorbent surface and (ii) prevents larger molecules from contact with the adsorbent completely. The coating significantly reduces efficiency of adsorption of molecules with molecular mass 1,000-20,000 (so-called 'middle molecules') and completely prevents adsorption of large molecules such as proteins, glycoproteins, lipopolysaccharide and circulating immune complexes which are responsible for a great number of pathological conditions and acute and chronic poisonings. These include poisoning with microbial toxins, autoimmune diseases, septic and toxic shock. Examples of such pathogenic substances are given in Table 1.

Table 1. Molecular mass of some toxins.

Toxin	Molecule	Mass, Da
Ricin	Glycoprotein	ca. 60,000
Botulinum toxin (A is most toxic)	Globular protein, 7.4 nm diameter	ca. 150,000
Staph aureus Enterotoxin B	Protein	27,000-28,500
Mycotoxins (aflatoxin B1, T-2)	Small organic molecules	< 500
Saxitoxin	Small organic molecule	300-370
Tetrodotoxin	Small organic molecule	319
Anthrax toxin	Three antigenic components, protein	240,000
Brucella abortus	Protein	30,000-94,000
Francisella tularensis (tularemia)	Outer membrane protein	43,000
Clostridium tetani toxin	Single polypeptide chain	50,000-100,000
Clostridium difficile toxins A and B	Protein	250,000-300,000
Diphtheria exotoxin	Single polypeptide chain	60,000
Streptococcal erythrogenic toxin	Protein	30,000
Clostridium perfringens (gas gangrene)	Protein	30,000
Verotoxin or Shiga toxin	Multi-subunit protein	32,000+5x7,700
a-Dendrotoxin from green mamba snake	59-amino acid peptide	7,100
Micrurus spixii (Peruvian coral snake) venom	Enzymes	10,700-73,100

In a number of microbial poisonings the major problem is not a micro-organism itself but rather its toxin which remains active in the medium even after the organism that produced it, was killed (examples include *C. difficile*, lipopolysaccharide from *E. coli* and others).

Another example of importance of large molecules in developing pathological processes is radiation effects on human body. Effect of ionising radiation, external or internal from incorporated radionuclides, is manifold. It generates reactive oxygen

species (mostly free radicals) which cause DNA damage, genomic instability, mutations and in severe cases leads to acute radiation sickness. Although precise identification of these products is hardly possible, they are known by generic names as radiotoxins, many of which are large molecules. Effective treatment of patients subjected to ionising radiation requires removal of not only radionuclides as such but radiotoxins as well.
Pyrolysis of a mesoporous polymer precursor followed by its activation allows production of AC with bimodal porous structure, in which mesopores of the original polymer are retained and micropores are developed in the course of activation. Polymer pyrolysed AC has excellent haemocompatibility which does not require additional coating and can be used in direct contact with blood. Several cases of the use of mesoporous AC in removal of large molecules are shown in the follwoing section.

Results

Mesoporous activated carbons have been used for the treatment of acute radiation syndrome induced in dogs, by passing the blood of irradiated animals through a haemoperfusion column (Table 2).

Table 2. Effect of haemoperfusion (HP) over activated carbon SUGS on acute radiation syndrome in dogs.

Group	Survival rate, %
Control (n=31)	3,2
HP 2 hours after irradiation (n=19)	68,4
HP 24 hours after irradiation (n=19)	62,4

Experimental conditions: Mongrel dogs, 8-12 kg weight, exposed to X-rays, with a dose that causes acute radiation sickness. All animals received antibiotics and human serum albumin transfusion as a basic conventional therapy. The 3rd group additionally had one session of massive saline transfusion, following diuretic furosemide prescription.

In addition to a higher survival rate, clinical symptoms of ARS were milder and the bone marrow syndrome was weaker in the experimental animal group. In these experiments there was no incorporated radioactivity, therefore the explanation of the protective action of haemoperfusion cannot be assigned to direct removal of radionuclides. Instead, activated carbon adsorbed products of radioactive destruction of natural proteins, DNA and other molecules. These radiotoxins are toxic to the organism and cause systemic endotoxicoses, severe inflammation and multiple organ failure.

Mesoporous phenol-formaldehyde based pyrolysed carbons efficiently removed pro-inflammatory cytokines TNF, IL-6 and IL-8 from human plasma. Figure 1 displays the representative timed adsorption data by the range of carbon adsorbents for the cytokine TNF only. Timed adsorption profiles for all three cytokines, recorded that control plasma contained no measurable TNF, IL-6 or IL-8, and the cytokine levels in the control cytokine spiked plasma (no adsorbent present) remained constant from 5-60 minutes. Carbon adsorbents 3 & 5 displayed the greatest cytokine adsorption capacity for all three cytokines with 87-100% removal within 60 minutes, adsorbent 5 displayed significant removal of all three cytokines compared to the control (Student t test, $p<0.05$, n=3). A cellulose coated AC Adsorba 300C showed low adsorption capacity towards these protein molecules [1].

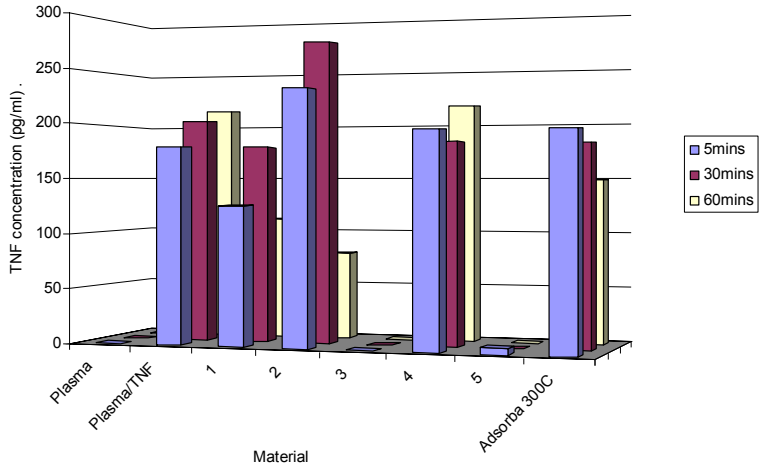

Figure 1. Adsorption of the cytokine TNF from human plasma. Plasma spiked with TNF was collected after 5-60 minutes.

References

1. Sandeman S, et al. 2005. Assessing the in vitro biocompatibility of a novel carbon device for the treatment of sepsis. *Biomaterials* 26: 7124-7131.

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