we are pleased to have dr sedona jackson

dr jackson is an assistant clinical

investigator within the neurooncology

branch at the nci here at the center for

cancer research nih

her research interest centers around the

evaluation of blood brain barrier and

malignant gliomas in the attempt to

transition

the disruption in order to improve

chemotherapy delivery

dr jackson received her medical degree

from eastern virginia medical school in

00 she completed a residency at

orlando health in pediatrics in 00

in 0 she completed a pediatric

hematology oncology fellowship at st

judes

then she did fellowship training in both

pediatric neurooncology and clinical

pharmacology at johns hopkins im sure

youll enjoy todays lecture

hello my name is sedona jackson im one

of the pediatric neurooncologists in

the neurooncology branch within the nci

and i have the pleasure to talk to you

today about drug transport across the

bloodbrain barrier and i termed it an

exciting night out on the town

as the bloodbrain barrier being the

club that you want to get to on your

exciting night out on the town and this

is within module two of drug metabolism

and transport

and in the principles of clinical

pharmacology 0 course

so think of the bloodbrain barrier as a

club bbb

think of it as you going out for an

exciting night out on the town

and imagine that you want to go see your

favorite celebrity or your favorite

entertainer and theyre going to be at

this local bbb club and it looks like

this with a whole bunch of lights and a

whole bunch of colors and hopefully not

seizure inducing but everybody inside

having a good time to see your favorite

entertainer or your celebrity

and

good thing to know about this bbb or

club bbb

is that its super selective not

everybody can get in

you have to be really strategic about

how you can go see your favorite

entertainer your favorite celebrity and

you want not just yourself to get in but

you want your friends to come along too

to see how great of a club it is to see

how great of an entertainer your

favorite entertainer is and you dont

want to be left on the outside like this

little girl here with your nose pressed

to the window not seeing all the fun

times or

being able to engage in the fun times

within club bbb

so you may ask what is so great about

this club bbb and how are you and your

friends going to get in so that you can

have a good time look how luxurious it

looks on the inside the the plush

seating it looks like theres a pool in

the middle of the uh the club i mean i

want to be at this club definitely this

is a picture not out not inside of the

us but we can all imagine and dream an

exciting night at club bbb

so

if you think about cloud ebb or the

bloodbrain barrier transport we first

have to go through what well be

discussing in this uh class so one what

are the cells that compose the

bloodbrain barrier so who can you find

at club bbb

what main factors allow for drug

transport what type of people can come

into club bbb

what is your criteria or what is their

criteria for allowing

certain drugs to get into the uh bbb so

how selective is this entrance who

dictates uh what gets in or what gets

pushed out

four so the bulk of this talk is going

to be on the modes of transport across

the bbb what clever ways can you get

into this bbb club

five what research up to date

has been done to open up or to cause

more permeability across the bloodbrain

barrier so finally you get in but you

want even more friends to get in so how

do how do you

strategically do that

and then

i can talk a little bit about what

research has been done or or what

availabilities there are to close the

the doors of the club bbb so how

temporarily how can you temporarily

close the doors to prevent your enemies

from getting in or from

other people who have come to see the

performance of this great entertainer

from getting out but you dont want to

lock them in there thats thats an

issue

so what is the bloodbrain barrier and

what is it composed of so ive talked

previously but its a selective

permeable brain interface its composed

of multiple cell types and they all

regulate which gets across the central

nervous system or the cns

so ill go into detail what the main

cells are and what they do so first

the cells that are involved if you look

at this picture here on the right hand

side youll see that the endothelial

cells the pericytes the basement

membrane the astrocytes the neurons the

microglia all play a role in this uh

neurovascular unit or nvu the

bloodbrain barrier but the endothelial

cells are the most important aspect of

the bloodbrain barrier so ill start

with that and so i term the endothelial

cells as bodyguards around that top

celebrity that youre there to go see

so these endothelial cells help to line

the vasculature specifically the

microvasculature within the brain and so

it dictates what drugs can come in and

out what solutes can come in and out

what agents can come in and out and if

you look at the blood vessels

specifically the capillaries within the

brain

you can see that the

the

tight junctions or the adherence

junctions the things that keep these

endothelial cells together

are much tighter in the brain than if

you look at any peripheral organs in the

liver or in the lungs those endothelial

cells dont have

as much tightness as as you would see in

the brain so thats something that

really

shows the difference between the brain

vasculature versus everything else

outside of the brain vasculature and

ill go a little bit more into detail

about how important these endothelial

cells are in regulating what gets in and

out of this club bbb

next you have these parasites so not an

extensive amount of research has been

done on pericytes but the parasites in

essence hug these endothelial cells

theyre pretty much buddy buddy and so

thats where the parasite name came from

parasite uh peri means around and site

means cell so i term these parasites as

security guards around your vip section

so you know the vip section is where

everybody wants to sit and and and have

a good time and chit chat with their

friends and look to see that everybody

else is having a good time so parasites

hug against these endothelial cells

that help uh protect against the

celebrity where the celebrity is also in

that vip section but the parasites uh

nicely communicate with the endothelial

cells to tell them

how that permeability should be how much

flow

the endothelial cells should regulate

amongst the

other cell types within the brain and it

dictates signaling with astrocytes and

with accompanied neurons and you can see

from this picture the communication

amongst the different cell types

next you have these astrocytes

astrocytes i termed as the super

friendly bartenders so you can see from

this picture the astrocytes are this

blue cell thats communicating with the

endothelial cells its communicating

with the pericytes has a little bit of

communication with the basement membrane

and also communicates with these neurons

so it is your friendly

bartender that has communication with

everybody making sure that everybody is

having a good time and getting serviced

and making sure that signals

communication is fluid so these

astrocytes are really integral to the

bloodbrain barrier

because its the specific globular in

feet that you can see that are touching

both neurons endothelial cells and

parasites that help with the

communication with all these different

cellular aspects they influence the

expression of efflux pumps on

endothelial cells transferrin receptors

on different cell types

and then transcytotic mechanisms on the

endothelial cells to be specific and

then when they communicate with neurons

they also support the energy supply to

be able to move across communication

across the synapses of neurons to

astrocytes

next you have the basement membrane also

called the basal lamina

it serves as the club manager or the

promoter to make sure that everybodys

having a good time

so you can see that the basement

membrane is in between the pericytes and

the endothelial cells and astrocytes

stabilizing things providing structural

and functional support in that

perivascular space

cells that are play minor roles so if

youve ever gone to the club not that

im a big club goer at least not in the

age that i am now but i did recall that

there was always this man or woman

walking around selling roses and youre

always like why is this man of this

woman selling roses like what is the

point of them

so

they become really clutch those people

and selling the roses if you ever see a

couple that comes into the club and

theyre having a good time and then for

some reason a drink gets spilled or

theres some kerfuffle that happens and

the guy whos selling roses comes about

and he says

do you want to buy a rose and so that

helps to kind of alleviate situations so

if you think about cells that play more

of a minor role in the bbb club

microglia neurons leukocytes

cells like these are not main components

of this club bbb but play a minor role

but they really pay more of a major role

when there starts to be issues so i

talked about there being a kaffel and

this person whos selling roses may try

to come in and be a peacekeeper at times

of inflammation or infection microglia

macrophages leukocytes

these uh minor playing role cells come

in they cause more of

inflammatory reactive modifying type

cells

and they come more to the surface

at the time of inflammation or intensity

or kerfuffle within the brain if you

want to say so they do help to alleviate

situations they sometimes exacerbate

situations you can think if theres a

altercation in the club and you see a

man come up and say do you want to buy

roses that person is getting in the way

and may have a little bit of altercation

with everybody else

so they do these cells play a minor role

but at the same time they may alleviate

or sometimes make situations worse

depending on what they are infection

tumors

plaques in the in the case of

alzheimers disease so

these are the main component cells of

club bbb

and its important that you know these

different cell types so if you dont pay

attention to any other uh slide in this

lecture this is the most important so i

highlighted it with my

purple square so these are the factors

that ultimately determine drug transport

so what dictates a good party so who do

you want there at the party so that

youre having a good time

so you always have that friend whos

like the life of the party easier to be

able to get into the party because

theyre like i want that person to come

into my club theyre gonna make

everybody else have a good time dancing

machines so i termed it as the bigger

the lipid content the better so the more

lipid soluble the drug the more likely

that itll get across and get into the

club bbb

but if you have that friend thats drink

too many energy drinks and theyre super

hyped up super charged up

the bouncer or whoevers at the front

door is not going to let that friend in

so you dont want a super or a large

amount of charge of a drug of a

substance

to get into the

club bbb and so thats just not

happening so charge at physiologic ph

really makes a difference about whos

getting in and whos getting out

so the presence of efflux transporters

so well go more into this in detail

later in the talk but you have to think

about it if you have muscular security

forcefully escorting attendees out then

youre not going to have a good party

and youre not going to have a good

amount of people inside of the club so

you always have to take into account the

type of transporters that you have

on the endothelial

cells pushing people out

next you have to think about

codependency or protein binding so this

picture on the left hand side details uh

total plasma concentration versus total

brain concentration if you think about

it in context if youre a drug thats

bound to a protein then youre more

likely and to stay inside of the blood

versus going to the brain interstitial

fluid or brain isf or brain

intracellular fluid brain icf so i said

codependency does not get you in the

building so if you think about the

concept of certain clubs where you have

men stand on one side of the line and

women stand on the other side of the

line in terms of security being able to

get into the club

if you have friends that came as a

couple and they

refuse to be separated to go into these

various security lines thats going to

be a problem and theyre not going to

get into the club so codependency is an

issue it wont get you into cloud bbb so

you have to think about that in context

of being unbound allows for more passage

across into the brain from the blood

circulation

and then right along with blood

circulation you have to think about

regional blood flow so a weak party

inside the building does not attract

people to come

from outside of the building so regional

blood flow being an issue if you have

blockage stenosis

ischemia from disease

certain infections hypoxia so varied

factors uh

play a role in regional blood flow being

low but you can think about it in the

context if youre regional if your

regional blood flow is low

if you have less uh permeability of

certain agents in one area then youre

not going to attract more people to want

to enter into that area so specifically

circulation or low

low amount of flow

so how do does the club bbb

determine what gets in because you do

have a selective permeable bouncer as i

would

state

so this selective permeable bouncer is

quite picky as to who he lets in

who is going to have a good time that

night so he wants only the nicest the

prettiest the most handsome and dance

loving people to get inside so of course

thats you and your friends right

so who enters and why

so quick entrance like i said before are

drugs with high partition coefficients

well ill talk about a little bit later

high lipid solubility agents molecules

that defuse passively so those are the

things that are going to get in quickly

and not have a problem to get in

the ones that are going to be a little

bit slower who like this uh

lady in the very front of the line she

looks like shes calling somebody shes

having the bouncer to check the list to

see if her name is on it

theyre going to have a little bit

slower amount of entrance because they

have a moderate amount of lipid

solubility or they may be

mildly charged or partially ionized

molecules so theyre going to have a

little bit of hangups at the door but

they may get in it just may take a while

the ones that will get turned away or

say no you cannot get in or again the

the friends that i said are really

charged upon those high energy

high energy drinks or they have a large

molecular weight or theyre not so life

i feel like theyre more hydrophilic so

those are going to get stopped at the

door

so if we talk about partition

coefficient coefficient

its important to talk about log p and

log ps so log p is really the measure of

how lipophilic a compound is and in

order to do that you measure the

ratio of octanol to water with octanol

being the lipophilic phase whereas water

being what it is the aqueous phase so

more likely that the

drug or agent of interest is soluble in

octanol the more lipophilic it is so if

you think about it in terms of a log

base scale agents with log p greater

than zero have a rapid chance transfer

or quick entrance

whereas agents with the log p

that have log orders less than zero or

negative one are limited and more likely

to be hydrophilic or polar compounds

and so you can see from this

picture on the left hand side its a

correlation between log p and log ps

so ps is a measure of bbb permeability

surface area so when you graph log p by

log ps

you see that theres a linear

relationship between the two

and you see that as you get higher in

your log p and as you get higher in your

log ps then youre more likely to be

some of these agents that at the top

right of the graph

that are very uh

would have very high

level of

drug entrance into club bbb

but there are always exceptions to the

rule and the exception is that there are

some drugs that are carriermediated and

the drugs that are carriermediated have

log high log ps

but low log p and so that

has them to be carriermediated

specifically glucose or ldopa

and it only applies to drugs this whole

graph really only applies to drugs that

are under the size of 00 to 00 dalton

with a few exceptions

so log p

lower

excuse me below the trend line

likely have a better threshold to cross

if theyre less than

00

there are some exceptions to the rules

such as this

bcecfam what has a hundred in 09

dalton

there are very few exceptions to the

rule and these arent drugs routinely

given

so the smaller the size the more lipid

soluble the more effective that the drug

is going to be able to cross and think

about that in terms of log p and log ps

so if you look at ps values two to three

log orders below the trend line those

are the ones that are actively effluxed

or if you look at ps values three or

four log orders above lipid solubility

trend line but two to three log orders

below log p

those are more likely to be carrier

mediated so dont spend too too much

time on this graph but log p and log ps

are important in determining what drugs

get across and the

lipid solubility context of how theyre

getting across

so the bulk of the talk bbb modes of

transportation so ill go into detail

about all these different um

means as to which

you or your friends could get across

into club bbb

until you think about paracellular mode

trans cellular mode transport proteins

eflux pumps receptormediated

transcytosis adsorbative transcytosis

and cellmediated transcytosis

and so this is a great picture in the

fact that it shows these uh endothelial

cells locked together by tight junctions

all the different various modes of how

drugs can get in and on the other side

of the endothelial cells on the brain

side it shows all the different uh major

and minor component cells that

are important in making up the blood

brain barrier

so one by one

so paracellular paracellular is the

means for aqueous pathway between cells

and i kind of term this as sneaking in

between of the wet side alley so you

always see in

movies or if maybe you go to certain

different clubs theres always like a

side alley that either the band comes

out of or comes into and sometimes the

main character of the story will sneak

in by means of this wet side alley so

thats this tight junction amongst these

endothelial cells thats the way that

watersoluble agents can get into the

brain

but they have to first cross through

what we call tight junctions or

adherence junctions these are the kind

of sticky type proteins that keep these

endothelial cells together and and dont

allow for other substances to get in

so

i said something earlier about tight

junctions and adherence junctions so

what are they so tight junctions uh

include zonular occludens sometimes

youll see them categorized as zo zo

or zo and theyre more of anchoring

proteins for clawed in sometimes

occluding

occluding clawdens and junctional

adhesion molecules are other types of

tight junctions they all pretty much

work together to have

transmembrane proteins

whichever they are to have their partner

on the other endothelial cell to come

together and kind of hug

and provide some kind of glue to keep

these cells together

additionally the adherence junctions

that just as important as the tight

junctions but not mentioned as much are

ve cad hearing

vascular endothelial

catherine and then platelet endothelial

cell adhesion molecule or pecan

and together all of these junctional

proteins work together to prevent

substances from getting through unless

theyre watersoluble substances

so

in the

time of disruption or at the time of

theres edema in the brain or swelling

in the brain

a lot of times these junctional proteins

will become disrupted and they come

apart

so thats when certain agents can get in

specifically more watersoluble agents

and even more water and so that aids in

some of the inflammation some of the

swelling that can come apart

and ill talk a little bit later about

studies ongoing to look at

modulation of these tight junctions to

cause more drugs to get into the brain

for certain conditions

so trans cellular mode of transport

thats the lipophilic pathway across the

cells

so this is the friend that i said is the

larger than life friend the one that the

bouncer sees them at the front door they

seem like the

would be the life of the party and they

easily get in so theres not so much

excitement to this slide theres not so

much excitement to these type of players

because its just easy entrance its

just a nobrainer in essence they come

in with passive diffusion these are the

lipid soluble agents theyre nonpolar

molecules and theyre pretty small and

when i say small less than 00 to 00

dalton and they easily just pass through

next you have transport proteins this is

a means for facilitated diffusion these

are the personal escort to the vip

section this is the

specialty bouncer that sees you and your

friends outside and they just kind of

take you as a whole and just take you

straight to that nice vip section

and so this is specific more for glucose

amino acids or nucleosides

and so its a sort of way of spontaneous

passive transport via these

transmembrane integral proteins along a

concentration gradient so its not

against its along with the

concentration gradient

and this is specific for glucose

transporters specifically glute and

glute those are the more highly

expressed transporters within the brain

and you always have to remember that

glucose is always needed for the br not

always needed in the brain for energy

so even if youre at a fasting state

your brain is still trying to work

towards getting more glucose to the

brain so you can think and be able to

function properly

so these glute and glute

transporters are very important within

the brain because they help to bring in

nutrients for energy and for metabolism

and so a lot of research has been done

about the the use of these transporters

specifically for

[Music]

diseases of brain cancer because

the cancers need glucose to be able to

function so if we cut down the supply of

some of the energy of the glucose

transport would be would we be in

essence affecting

the activity or the energy of normal

brain cells and thats a yes

next you have to think about other

transporters that use facilitated

diffusion and those are amino acid

carriers and monocarboxylate

transporters so for amino acid carriers

an example is the lat or glutamate with

eatss which are excitatory amino acid

transporters

so if you have large neutral amino acids

like levodopa its going to use the lat

transporter but excitatory amino acids

are going to use the

eats transporters thats a lot thats a

mouthful so this picture on the side

just shows for one substance thats

glutamate and thats these blue circle

spheres

and how glutamate is transported amongst

the endothelial cells the neurons and

the astrocytes all key players of the

bloodbrain barrier

and how glutamate transport occurs with

the use of these

eat

one two or three transporters on these

varied cells

additionally when the glutamate gets

broken down via the tca cycle and then

gets converted to lactate the mct or the

monocarboxylate transporters move that

lactate into the blood circulation

and yet the mct transporters or the

monocarboxylate transporters are

important also for ketone bodies and

other metabolites

and then lastly you have to think about

nucleosides they also use this form of

getting in specifically adenine and

adenosine which are key

for

all cellular processes and solute

carriers the slc superfamily sometimes

solute carriers get mixed in with the

efflux transporters which ill talk

about next

but in essence solute carrier super

family

carry organic acids or weak organic

acids into the cell so organic anion

cation transporters are termed oat or

octs and the specific substrates that

they help to bring in are nonsteroidal

antiinflammatory

drugs

hormones or drug metabolites

next you have these efflux pumps so this

picture doesnt do justice for

the generation of

what abc transporters are but i know in

another talk that you have gotten

extensive

experience or youve become an expert

now on what abc or multidrug resistant

proteins are so i wont go too too much

in detail but just know that this

picture is not

sufficient to show the amount of atp

generation and the fact that these are

transmembrane

proteins that help to pump things out of

the cell

and are really

bulky and really do a lot of work so i

term these as muscular security or

muscular security guards forcing or

escorting attendees out so theyre

throwing people out like like

throwing them out theyre falling onto

the concrete cant come back in type

muscular security

and theyre doing so with the addition

of atp hydrolysis so atp to adp and

theyre moving against or across the

concentration gradient so drugs that are

lipophilic but a lot of times polar

get swept out

with these abc transporters and theres

a large family of abc transporters this

is just a small

picture of the ones that are present

but i think the total now is greater

than 0 abc transporters that are

present all throughout the body

but there are a small amount that have

been identified within the brain and so

these are just a few in this picture

here off to the left hand side

but there continues to be research on

the amount of transporter expression and

function within the brain at the times

of normal state as opposed to infection

or diseases

so you can imagine depending on what the

drug

presence is that there may be more

expression or more function of these abc

transporters

so

there are varied transporters being

expressed within the brain

with the main ones being pglycoprotein

also termed abcb and bcrp

also termed abc g and bcrp im sure you

learned from the previous talk is breast

cancer resistance protein and these are

large glycosylated proteins

theyre substrate specific

and they often are substrates that are

lipophilic but they have high charge so

of course like i stated before you dont

want that friend that has a lot of

charge to get into the

club bbb but if they do

your friendly

muscular

security guard is going to push or force

them right on out

and a lot of research has been done

specifically at the nih

with

goddessmans group

to look at transporter expression and

the impact of inhibiting these

transporters for allowing more drugs to

get to where we want them to go for

issues of disease or dysfunction

so not to go too too much in detail

because you can read on your own that

these different transporters peak like a

protein mrp mrp which are

multidrug resistant protein thats what

mrp stands for

mrp mrp bcrp

again have their own substrates that

they

help to transport out and a lot of those

substrates that have been identified

have been in the oncology world because

as a neurooncologist we want to be able

to give drugs that

impact the growth of the tumor cells but

in essence get to where they want to go

but because our brain is a little bit

smarter than us

it utilizes these transporters to

transport things out so its a constant

tug of war when we try to think about

the optimal amount amount and the type

of therapy you want to give for certain

brain cancers

so then next you have receptor mediated

trans cytosis thats like having a

friend on the inside of the door stating

theyre with me so you have your friend

thats already on the inside right about

to to have the concert or your favorite

celebrity walk through the door and they

see you on the outside and they say

shes with me or hes with me come on

inside so this is your friend saying you

know come with me ill get you in no

problem

and this is in in essence the

receptormediated transcytosis so you

have somebody on the inside working to

bring you in and thats mainly uh

catherine clathrin or caveolin dependent

endocytosis or an endosome

that aids in getting these drugs or

these molecules in

and once that endosome kind of

encapsulates that drug or encapsulates

that agent then you have allowance of

transcytosis which is that endosome

moving through these endothelial cells

and then can go uh kind of be absorbed

on that abnormal side and then that drug

or that agent gets entered into the

brain circular the brain sometimes you

have degradation of these uh agents of

these drugs via lysosomes and thats

okay because thats just the fate of

things

but thats a better depicted in this

next picture so just a warning this is

not at all a bbb picture but i thought

it was a great uh descriptive way to

show how

insulin specifically gets taken up by an

endothelial cell and then transported to

a skeletal blood vessel skeletal tissue

so you can see in green thats these

endothelial cell

excuse me you can see in green that you

have the insulin

drug or insulin agent molecule that gets

taken up by the insulin receptor it gets

endocytosed and thats clathrinmediated

it undergoes transcytosis with the

insulin

still attached to that receptor

and then you have

absorption to that abnormal side the

endo in the insulin gets released it

gets taken up by the receptor on the

skeletal muscle and then that generates

for glucose to come in and give your

skeletal muscles some energy to move and

and be able to go about

so again this is not the the brain of

the bloodbrain barrier but i thought it

was a great uh show of what happened

with transcytosis so this is just one

agent that works via transcytosis but if

you look at

amyloid beta which is a big of a focus

in the alzheimers world with amyloid

beta predominance or

[Music]

increase the expression and presence of

amyloid beta

that gets taken up by lrp a receptor on

endothelial cells again gets endocytose

and its clathrinmediated

theres a lot of processes you dont

need to go too too much in detail about

but theres a late endosome and a

sorting endosome and and some

level of destruction with lysosomes

so

thats not so much significant in terms

of this talk but this is again another

picture to show that

amyloid beta

uh gets taken in by lrp gets endocytose

you see this nice transytosis within

deposition into this blood vessel here

for further circulation

so its great because there are all

these different agents that get taken

out by receptormediated trans cytosis

such as insulin which i showed before

transferrin

lipoproteins leptins amyloid beta tumor

necrosis factor alpha and egf and there

are many many more and theres a lot of

research being done now to look at

how

drugs nanoparticles other agents can

utilize this means of receptormediated

transcytosis

of receptors that we know

easily or routinely take in these agents

to try to bring in drugs chemotherapy or

otherwise into the brain or the

circulation

next you have absorptive transcytosis

think about it as celebrity paparazzi

gaining access via vip press pass so the

celebrity

paparazzi this

female or male with this large

camera strapped to their chest they say

i have this vip press pass and i have my

large camera please just let me in i

dont even need to pay entrance you know

im here to just take pictures

so its like another nobrainer access

just gets in and these are usually

exclusive to cell penetrating peptides

so these are positively charged

peptides that

nicely attract to the negatively charged

phospholipid bilayer of the endothelial

cells so they get reintegrated via

vesicular transport

via the ablominal side and then they get

just get delivered to the rest of the

the brain or the circulation

and its usually

its usually

reserved for cat ionized

albumin or plasma proteins specifically

histone or avidin

and its often seen with conjugated

lipid nanoparticles so like i said

before

theres been a lot of research into how

to get

how to

understand or the understanding of drug

transport and how we can manipulate that

known understanding so that we can get

our drugs of interest in so

nanoparticles have been more

more of an exciting area because if we

use

nanoparticles with receptor mediated

transcytosis or absorptive transcytosis

means then we can get more of our drugs

that usually dont cross or usually get

pumped out via this way of transcytosis

of receptormediated or absorptive

next you have cellmediated transcytosis

i term it as the undercover officer with

a concealed weapon

so he or she is going to come in with

their concealed weapon uh be it the drug

or agent or or substance of interest

they get into the club no problems and

then they release that drug or substance

or agent

and this is usually

a cell media transcytosis where you

serve as a trojan horse to allow drugs

or molecules to cross the bbb and thats

usually your monocytes your macrophages

your neutrophils and those like i stated

before are the ones that are recruited

during inflammation or times of

issues or concerns either infection or

or

tumor or plaque formations

and you sometimes will see them with

drugs or drug liposomal conjugates

nanoparticles or stem cells that are

giving some antibody for delivery so

like i said this is your undercover cop

with a concealed weapon coming in giving

something for delivery thats important

but it needs to be concealed in a

certain way like a trojan horse

so some of the disadvantages of this

means of uh transitosis is that

sometimes you can have poor drug loading

and so that the drug doesnt get in like

you wanted to

you can sometimes have premature release

of your loaded carriage so that the drug

doesnt get to where it uh needs to get

to because it gets released before it

can even start to cross through the

endothelial cell

and then sometimes you have inability of

the cargo to selectively reach the

destination so all those disadvantages

come in in

a lot of the studies now being

looked in for delivery of antibodies or

being looked at as delivery of drugs

so

if you use one of those means and you

finally got in

there have been

issues where either you get pumped out

or you dont want to get pumped out or

you finally get in but how do you open

the door so that more things get in or

do you get more of your friends into

this club bbb so thats been more of

research

in the last 0 to 0 years in conditions

such as brain tumors or infectious

lesions specifically space occupying

lesions with potential invasiveness so

ugly brain tumors that can invade or

metastasize or metastatic brain tumors

so if you think about it we give

chemotherapy

through an iv or through a central

intravenous line

and we want the drug of interest either

orally

we want the drug of interest to get to

the brain without directly giving the

drug to the brain

well you saw all these means of how

things can get pumped out or depending

on what the drug looks like it doesnt

get in

and so this has been a lot of interest

in research to increase permeability or

how to circumvent the bloodbrain

barriers so that we get these drugs in

so there have been a lot of studies to

look at mediators that can increase

permeability so these are

factors that are already produced by the

body

that dr abbott was able to list out and

say

these agents

know we know can impact these tight

junctions or we know can impact

different ways of transport and allow

more drugs to get in so these are just

normal

humoral agents

that can increase blood brain barrier

permeability so more and more studies

have gone into looking at these agents

and other agents like these that can

impact drug transport specifically for

space occupying lesions

and so

in addition to those mediating agents

that can increase permeability theres

been a lot of research on nanoparticles

microspheres albumin or lipidbased

agents or mannitol specifically to

disrupt tight junctions to increase

delivery so i thought this was a great

schematic thats

um part of this frontiers and oncology

kind of review paper back in 0 that

talked about the different modes of

drug delivery

and how it showed that

i think theres a total of four that

they list here but theres multiple that

people have researched on how to

increase drug delivery and sometimes

theres been uh agents to basically

circumvent the blood brain barrier

and thats been agents such as a

biodegradable wafer that the

neurosurgeon would place at the time of

surgery

and that biodegradable gradable wafer

has chemotherapy impregnated in it and

so over time that chemotherapy diffuses

out now i hadnt has not been shown to

be so much effective over time but its

a great concept to think about basically

circumventing all those things or all

those issues of what i discussed earlier

for barriers of drug delivery and then

just basically taking the drug straight

to the source without having to worry

about other options

theres also other

research looking at convection enhanced

delivery intranasal delivery

and and microchips use

and then theres also

the thought of what if you need to close

the doors temporarily to prevent other

people from getting in your enemies or

from people from exiting out

so if you think about that in the terms

of conditions such as early alzheimers

or a head injury or stroke or aging so

these are conditions where theres some

induction of acute or chronic blood

brain barrier leakage

and so you have these this leaky

vasculature maybe because of

inflammation maybe because of trauma

so in terms of early alzheimers disease

theres a lot of inflammation and

theres a lot of cognitive decline but

that goes with the amount of plaque

formation that goes with the amount of

bbb leakage

in the

event of head injury either acute or

chronic or repeated

such as in the instance of

football or

other type of sporting events

that repeated injury or that one time

injury really can affect regional

differences of vasculature leakiness

that can be assessed with serial head

imaging or serial neurologic exams

but a lot of research has been looked at

to how we could prevent either or

stop the amount of leakage that occurs

with these incidents we also see a lot

of leakage

with the impact of ischemic stroke due

to endothelial damage due to hypoxia or

lack of oxygen in certain areas

depending on where the stroke is or the

time course of the stroke

and even aging has been shown to have

small amounts of leakage over time and

so you see cognitive decline that goes

with that so sadly theres not a ma not

much of

agents to attenuate or decrease the bbb

leakage or

increase bb abu permeability you see

with these conditions

and so these patients are left of giving

supportive care supportive support of

the varied neurologic sequelae that

comes from this leakage so thats

continuing research ongoing

so just as an aside there are various

clubs for you to try to get into that

luxurious club that i explained in the

very beginning that had the pool in the

middle and the the nice plush seating so

in addition to the blood brain barrier

theres a blood retinal barrier that the

blood cerebral spinal fluid barrier

uh the blood chloride plexus barrier the

blood testes barrier the blood lymph

barrier the blood thymus barrier the

blood air barrier the blood biliary

barrier theres so many different

blood

barriers theres so many different

types

this

talk is just exclusive to the blood

brain barrier which i have a deep

passion for but theres so many other

different types of barriers theyre not

as

i wouldnt say theyre as detailed

in terms of

the tightness of the endothelial cells

and limiting restriction and these uh

forceful bouncers at the front but

theyre just as important and there have

been a lot of research thats been done

in these various

various barrier clubs but theyre not as

cool as the bbb club i have to say

so i thought this was a great picture um

by zao in a cell paper that was put out

in 0

and in essence it goes through all the

the detailed

transporter

functions of the main key players of the

bloodbrain barrier im not going to at

all describe this picture in detail but

im a visual learner as you probably can

see from the the way that i

gave this talk and the fact that i had a

lot of pictures and a lot of animations

but i thought this was a great picture

that

his group was able to show in terms of

transport and key mediators of the blood

brain barrier and bbb in depth so if you

didnt get enough from this talk then i

would say to refer to this

review paper because it goes into a lot

of detail in terms of key players and

and what they do so in summary the bbb

is a selective wall that protects the

brain

uh drug transport across the bbb is

dependent on many factors specifically

size specifically charge lipophilicity

polarity protein binding and research is

ongoing to influence permeability for

varied cns disorders

id like to thank you for joining me

today to talk about the bloodbrain

barrier and the transport across it and

if you have any questions regarding this

matter please email me