Systems Medicine Lecture Notes

Uri Alon (Spring 2019)

https://youtu.be/Vblo9lm2p8c

Lecture 12

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Addiction

Addiction is a world epidemic

Addiction to substances causes suffering and dysfunction in relationships and work. In addition to ruining a person's enjoyment of life, addiction can end life by overdose. Major addictions include abuse of alcohol, cocaine, nicotine and amphetamines. Addiction to opiates, including heroin and prescription painkillers, has quadrupled in the past 20 years, and opiate overdose is a leading cause of death for teenagers (Fig 12.1). Diseases associated with alcohol (heart disease, liver fibrosis) and smoking (lung diseases, cancer) are major killers of adults.

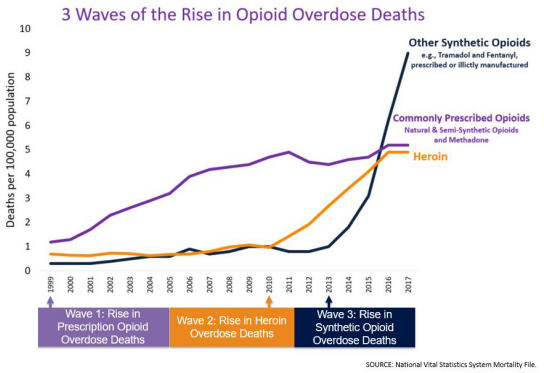

Figure 12.1

I tried to find songs about addiction for this lecture; it was actually hard to find songs *not* about addiction. J.J. Cale (Fig 12.2) wrote

"If you want to hang out,

you got to take her out, cocaine.

If you want to get down,

down to the ground, cocaine.

She don't lie, she don't lie she don't lie,

cocaine."

Figure 12.2

By "she don't lie" he might have meant that the addicts world view shrinks to the one truth of obtaining the substance. Things you once enjoyed, like hugs and chocolate, don't bring as much joy anymore.

Addiction shows a universal curve

Different addictive substances work in different ways on the brain. Despite these differences, they all share a temporal sequence. In this **universal addiction curve** (Fig 2) time is on the x axis and craving is on the y axis. At first there is the **initiation** phase. The substance produces a sense of **euphoria-** an emotional high. This creates **positive reinforcement**, an urge to use the substance again.

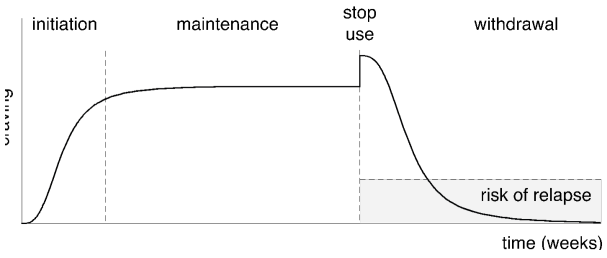

Figure 12.3

The euphoria only lasts a few weeks. Now, to gain the same euphoria one must increase the dose. This is called **tolerance**. Stopping to use the substance causes awful symptoms called **withdrawal** symptoms. These include anxiety, depression, tremors, pain and vomiting. To avoid withdrawal symptoms, one needs to keep taking the substance just to feel normal. This is the **maintenance** phase. Now one is dependent on the substance, fully addicted.

Maintenance is thus reached because of two types of reinforcement: positive reinforcement due to euphoria, in which the person learns to seek the substance, and negative reinforcement due to withdrawal symptoms, in which the person learns to use in order to avoid feeling awful.

The last phase occurs when stops using, the **withdrawal phase**. In the first few hours and days withdrawal symptoms are very strong. They then reduce in intensity but persist for several weeks. Then there is apparent recovery. The next few months are a sensitive period that has risk of relapse- going back to use. After a year or so the person has adapted and craving is gone. There is a lifelong risk of relapse, however, especially in times of stress or when the people and places from the maintenance period are revisited.

Treatment for withdrawal includes therapy, peer-groups that provide commitment and hold a person accountable, and motivational interviewing which can identify each person's motivations and obstacles for recovery. Medications also help, such as medications that block the opioid receptors.

Thus, rehab centers typically take the person for several weeks to match the timescale of withdrawal - such as the 70 days in the song by Amy Winehouse (Fig. 4)

"They tried to make me go to rehab

I said, "no, no, no"

Yes, I've been black

But when I come back, you'll know, know, know

I ain't got the time

And if my daddy thinks I'm fine

He's tried to make me go to rehab

I won't go, go, go

I'd rather be at home with a Ray

I ain't got seventy days"

Figure 12.4

In this lecture we would like to understand the addiction universal curve. What is the origin of the different phases? And where does the timescale of weeks for tolerance and withdrawal come from? This timescale is puzzling because the effects of the substances on neurons, neurotransmitters and receptors are reversed within hours to days after stopping use.

Addictive substances act on reward centers of the brain

The mechanism for each substance is different. Let's focus on opiates, the most addictive substances, like heroin and morphine. Opiates bind to opiate receptors on neurons and modulate their function. They inhibit neurons that inhibit other neurons that produce dopamine in reward centers of the brain. This effect leads to euphoria. They also act on neurons in pain centers in the brain and spinal cord- and there, opiates act as **pain killers**.

The body make natural morphine, called endogenous morphine or **beta-endorphin**. These are made after exercise for example, contributing to 'runners high', or during the fight-or-flight response, to act as painkillers and euphoria-generators. External opiates include the addictive substances are made by poppy plants, opium and its derivative heroin. In this way, plant mimic the endogenous molecules to manipulate animals. Synthetic opiates are taken as powerful painkillers. They are extremely addictive because the reward centers signal the person to learn to take them.

Other substances also affect neurotransmitters. Cocaine increases the concentration of dopamine and other neurotransmitters in reward centers by a different mechanism from opiates- cocaine inhibits reuptake pumps (like SSRIs of the previous lecture). Alcohol increases the effect of dopamine and other neurotransmitters by yet other mechanisms, such as enhancing receptor binding.

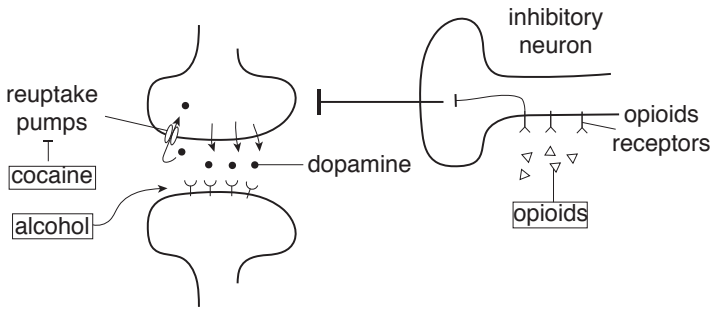

Figure 12.5

Tolerance means that the dose needed for euphoria gradually rises

A universal feature of addiction is tolerance, in which the dose needed for the same effect gradually rises. The response to a given increase in dose shows diminishing returns. Going from average use level 1 to 2 and then from 2 to 3 shows smaller and smaller pulses of euphoria (Fig 12.6).

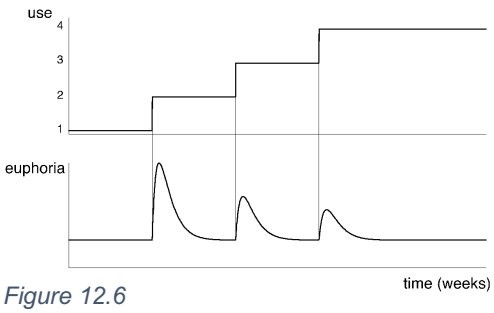

Figure 12.6

That is why users increase the dose, until hitting a maximal tolerable level (or money runs out). But constant euphoria is never attainable. As Muddy Waters sings (Fig. 12.7)

> *"If the river was whisky, and I was a diving duck,*
>
> *If the river was whisky, and I was a diving duck,*
>
> *Id dive right to the bottom, never would I come up."*


Figure 12.7

Theories for tolerance focus on receptor downregulation, but this cannot explain the timescale of weeks

The current theory for tolerance is that excess amounts of neurotransmitter X such as dopamine causes the receptors for X to be removed from the cell surface, or chemically modified to bind X more weakly. This is called **receptor downregulation**. Thus, the cells adjust their sensing of X to restore homeostasis of activity levels.

Receptor down-regulation takes hours, and is reversible: once levels of X go down again, receptors return to their normal levels within hours to days.

Such receptor downregulation can explain the early effects of withdrawal: after a long period of use, there remain very few receptors on the neuron surface. Stopping use makes X levels go down to normal. But there are so few receptors that this level of X translates to sub-normal neuronal activity. It takes hours to days for the receptor numbers to adjust and activity to return to normal.

The receptor theory explains the strong symptoms in the first hours and days of withdrawal. But it cannot explain why it takes weeks for tolerance to develop in the initiation phase and why withdrawal symptoms last for weeks. We need a slower physiological process with the timescale of weeks. Our explanation, as in the previous lecture, will focus on the HPA pathway.

All addictive substances activate the HPA pathway

A common feature of all of the addictive substances is that they activate the HPA axis, by making neurons in H secrete the hormone x_1, CRH. This includes nicotine, alcohol, opiates, cocaine,

amphetamines and cannabinoids (Fig 12.8). Each substance activates the HPA axis by a different mechanism. The activation is sizable: people with alcohol abuse show about 3 times more average cortisol (averaged over weeks using hair cortisol measurements) than controls.

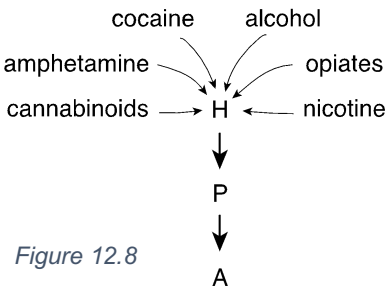

Figure 12.8

The HPA axis plays a key role in addiction because **HPA is a major producer of beta-endorphins.** The hormone x_1 causes the pituitary P to secrete hormone x_2, and at the same time, to secrete beta-endorphin (Fig 12.9). This linkage is because x_2 and beta-endorphins are both made from the same precursor protein called POMC (Fig 12.10). This precursor protein is cleaved by special enzymes in the cell to make x_2 and beta-endorphin. The evolutionary rationale is that responses to events that stimulate HPA activity, such as exercise and fight-or-flight threats, benefit from the pain killing and euphoric effects of beta-endorphins along with the effects of cortisol.

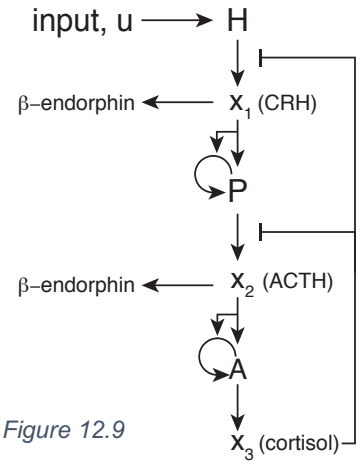

Figure 12.9

The rewarding effects of beta endorphin contribute to positive reinforcement: the person learns to seek the substance during the initiation phase.

From now on, we will use the fact that x_2 and beta endorphins are produced in a 1:1 ratio, and consider the dynamics of beta endorphins produced by P as equal to that of x_2 in the model. In addition, x_1 (CRH) also induces production of endorphins in the brain, made by POMC neurons in H (Fig 12.10).

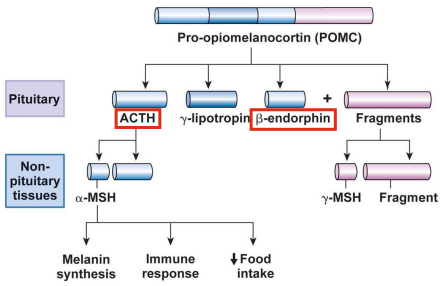

Figure 12.10

HPA is deregulated during addiction, with a blunted x2 response

During addiction and withdrawal, experiments show that the HPA pathway is deregulated. This is best seen using classic test of the HPA axis, called the **CRH test**. Hormone x_1 (CRH) is injected, and hormones x_2 and x_3 are measured at several time points over the next two hours (Fig 12.11). In control subjects, both x_2 and x_3 rise after the x_1 injection (time of injection is shown by an arrow in Fig 12.11), and then decay. In people in the maintenance phase of addiction, or right after stopping use (acute withdrawal), cortisol x_3 is higher than normal, reflecting the activation of the HPA pathway. In contrast, x_2 responses are lower, a so-called "**blunted response**". This indicates that a given stimulation of the axis provides a lower beta-endorphin reward. This blunted response is the basis for the reduced pleasure from things that used to give joy that is experienced during addiction. This reduction is called **hedonic dysregulation.**

After about a month into withdrawal, the CRH test shows that x_3 returns to normal. Interestingly, x_2 is still blunted (Fig 12.11, right hand panels). This phase is called mid-term abstention. Only after 6-9 months does x_2 response also return to normal, and the axis is no longer dysregulated.

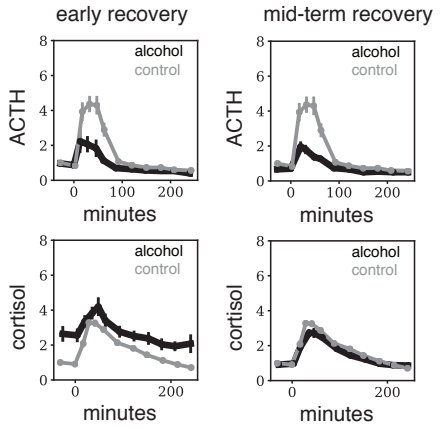

Figure 12.11

HPA dynamics show long-lasting tolerance with fold-change detection

Addiction can thus be modelled as a chronic increase in the average input to the HPA axis, u. We can think of a long constant input of u averaged over weeks. Solving the model on the slow timescale of weeks shows that the hormones x_1, x_2 and x_3 rise (Fig 12.12). Within weeks, however, x_1 and x_2 both return to baseline despite the increased input u. This feature is called **exact adaptation.**

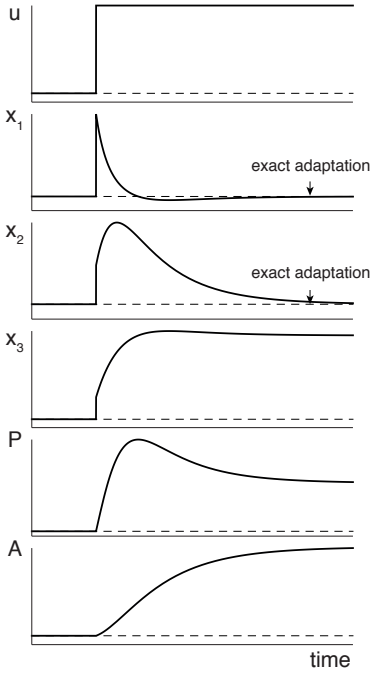

Figure 12.12

The important meaning of exact adaptation for addiction is that the euphoria produced by the substance lasts only for a few weeks. Euphoria gradually vanishes and then vanishes because x_1 and x_2 levels adapt, and with them the levels of beta endorphins, despite the continued presence of stimulus u. This aligns with is the phenomenon of tolerance.

The reason for exact adaptation is the growth of the glands A and P (Fig 12.12), which makes x_3 rise to exactly shut off x_2 back to baseline. The timescale of the glands, on the order of weeks, explains the slow timescale of tolerance.

Mathematically, exact adaptation of x_2 arises from the equation for the size of P

$$\frac{dP}{dt} = P(x_2 - a_P).$$

The only way to reach steady-state is when x_2 returns to its baseline level, $x_2 = a_P$. When substance is used, x_2 initially rises above baseline making P gland grow (positive dP/dt). A similar effect for x_1 makes A grow. The growth of P and A make cortisol levels rise, which inhibits x_2 production and makes x_2 return to baseline. A similar equation guides x_1 to adapt back to its baseline, $dA/dt = A(x_1 - a_A)$.

What happens if the substance dose is further increased? Increasing dose leads to a new pulse of x_2, which also eventually adapts. The response to a given increase in dose shows diminishing

returns. Going from input level 1 to 2 and then from 2 to 3 shows smaller and smaller pulses of x_2- we saw this graph before when discussing tolerance (Fig 12.6).

The HPA circuit shows that in order to recover the same euphoria, one needs to increase input u to ever larger doses. In fact, one can show that the HPA circuit shows response to *relative* changes: the x_2 pulse is the same only when the dose is increased by the same factor. To replicate the pulse of x_2 due to a rise of u from 1 to 2, one needs to raise u from 2 to 4 (Fig 12.13). Both steps have a two-fold change. Thus, to maintain euphoria requires an exponential increase in dose, from 1 to 2 to 4 to 8 to 16 and so on. Such an exponential increase cannot last long because one eventually hits a ceiling of toxicity.

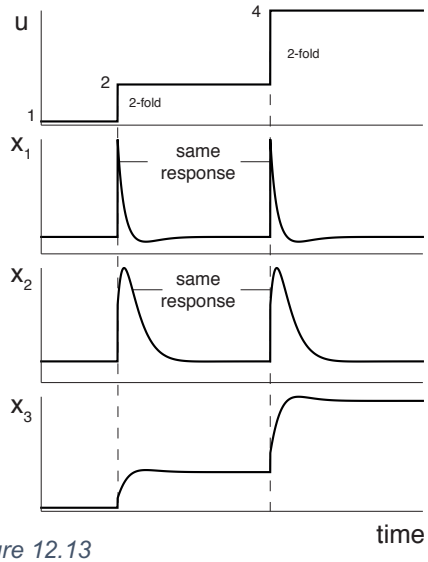

Figure 12.13

The HPA model shows withdrawal that takes weeks, and medium-term abstention with normal cortisol but blunted x_2.

To model withdrawal, we set u back to normal levels after a long period of high u. The HPA axis glands now gradually adapt back to normal size over months (Fig 12.14). Interestingly, the P gland adapts faster and reaches its baseline in weeks while A is still large. P then shows an undershoot, creating a period of months where A is normal but P is small. Then P adapts and the HPA axis is fully normal.

This dynamic creates two zones of withdrawal. In the first, early or acute withdrawal, both x_3 and x_2 are dysregulated, with high x_3 and blunted x_2 as found in the CRH test (Fig 12.11 mid panel). In this zone, withdrawal symptoms are most severe. The timescale of weeks arises from the time it takes A to normalize.

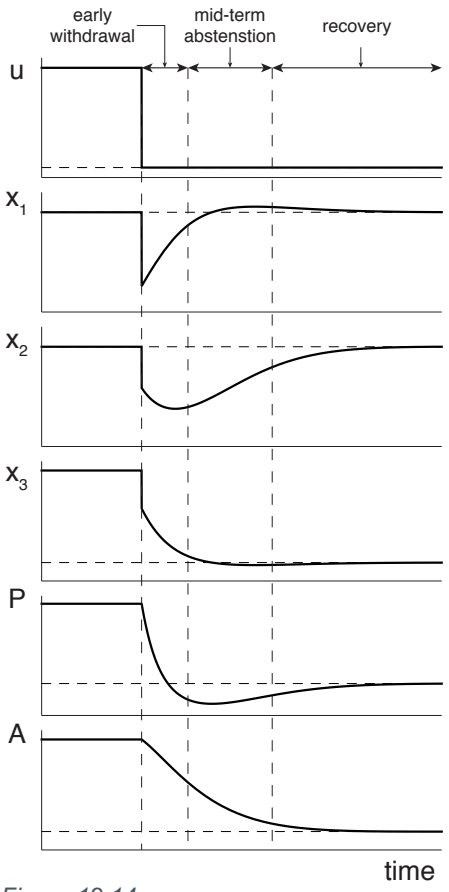

Figure 12.14

The dynamics also reveals a medium-term abstention zone (Fig 12.14). In this zone, x_3 responses are normal, but x_2 (and hence beta

endorphin) is blunted. In this zone, one expects hedonic dysregulation, where a stimulus u gives less beta endorphins than normal. There is less enjoyment of things that use to give joy.

One may speculate that this midterm abstention zone is prone to relapse. Low endorphins may cause anxiety and pain. Since endorphins are low, a person might seek ways to simulate the HPA pathway to recover x_2 levels- namely returning to the habit of use.

The HPA model can thus provide a mechanism for why withdrawal takes weeks.

Relapse may be triggered by people and places associated with previous substance use

This section is a walk down tangent boulevard. We note that the brain has a clever way to react to habits of substance use. Consider alcohol, which acts to lower heart rate and blood pressure. If a person has a habit of drinking at a given time and place, say 6pm in the living room, the brain learns that pattern. At 6pm in the living room the brain raises heart rate and blood pressure, to counter the expected effect of alcohol, and thus to maintain homeostasis. With cocaine which raises heart rate, the brain instead lowers heart rate at the habitual time and place.

If now a person at 6pm in the living room has no alcohol, the brain still raises heart rate and blood pressure. This feels awful, and creates negative reinforcement to seek alcohol.

Conversely, if alcohol is consumed at an unfamiliar time and place, say at midnight at a party, there is no compensation by the brain. The dose one usually drinks can cause an overdose.

Finally, if a person has recovered and stops drinking, but returns to an old situation associated with drinking, the brain might again cause the compensation, and the person will feel awful and might be tempted to return to drink. Of course, the psychology of all this is much more complicated than this discussion.

Addiction is the dark side of a stimulation-taxis function of the HPA axis

In this course we like to think of each pathological condition as a fragility of an essential physiological process. In the case of addiction, this essential process is the ability of the HPA axis to guide behavior to beneficial regions.

Let's start with the fact that cortisol levels have an optimal middle range, as described by the inverse-U-shaped curve of the previous lecture (Fig 12.15). Low levels of x_3 cause fatigue and depression, mid-levels generate energized and concentrated focus, and very high levels cause depression and anxiety. Thus, organisms seek behavior that leads to stimuli u that keep cortisol at its optimum, namely challenging yet rewarding behavior.

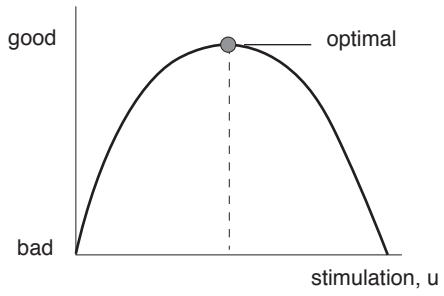

Figure 12.15

What system can guide behavior towards the goal of optimizing u? This search problem can be thought of as a search in a hypothetical **space of behaviors**. One seeks the region of behaviors that provide optimal u. Each behavior in this space brings some averaged stimulation input u, and thus u can be plotted in this space as a kind of topographical map with hills and valleys (Fig 12.16 shows a hill with the optimum at the top). Finding the best behaviors means climbing gradients of u in behavior space.

An analogous search problem is solved by bacteria - single-celled organisms that can swim in search of food and other attractant chemicals, and away from noxious chemicals. Bacteria detect attractants using receptors, and can climb spatial gradients of attractant. For example, if a pipette with attractant such as the amino acid aspartate is placed in a dish of bacteria, they swim and accumulate in the pipette. This process is called **chemotaxis**: you see a chemical and call a taxi.

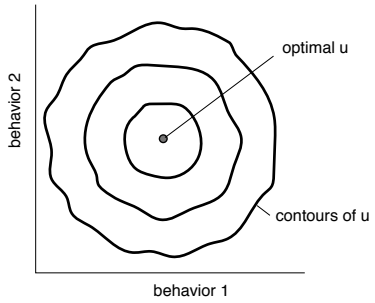

Figure 12.16

Bacteria achieve this feat despite huge challenges: they are so small that if they try to swim straight for ten seconds, Brownian noise deflects them by 90 degrees on average. They have no notion of where they are. They are too small to sense gradients across their one-micron body. But still they accurately find the pipette across five orders of magnitude of attractant concentrations, climbing tiny gradients as small as one molecule difference between their head and tail over a background of 1000 molecules per cell volume.

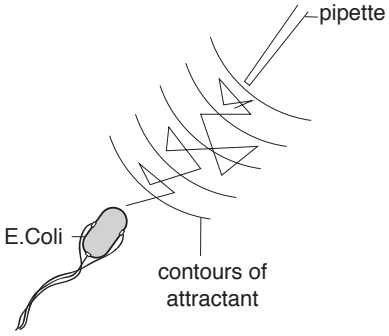

Figure 12.17

Bacteria perform chemotaxis using a simple algorithm: if things get better, don't change direction. If things get worse, randomly change direction. They can control only the frequency at which their motors make random changes of direction. Thus, bacteria do a random walk, swimming for about a second and then changing directions randomly in what is called a **tumble** (Fig 12.18). They measure the temporal changes in attractant levels. If attractant rises with time, they suppress the tumbling frequency and keep swimming in the same direction. If attractant levels drop with time, they tumble, hoping to return to the right direction.

Figure 12.18

Bacteria do chemotaxis using a biochemical circuit inside the cell that analyzes the input from the receptors. The chemotaxis circuit is one of the best understood circuits in biology, and figuring out how it works was one of the pioneering accomplishments of systems biology. Bacteria use separation of timescale, with a slow process that accumulates to provide exact adaptation and fold-change detection of attractant stimuli.

Thus, providing a step of attractant makes bacteria stop tumbling no matter what direction they are headed (Fig 12.18). Then after a few minutes, bacteria realize they have been fooled and start tumbling again. They response to a step of input with a pulse of output (tumbling frequency), showing exact adaptation.

In fact, the equations for the biochemical circuit inside the bacteria are mathematically identical to equations in the model for the HPA axis. In bacteria, the receptor binding constant K for attractant can be tuned by a slow process of receptor modification called methylation that takes minutes. The equation for K is $dK/dt = K(x - a)$, where x is the tumbling frequency. This provides exact adaptation of x back to a. An analogous slow variable in the HPA axis is the gland size P, governed by the equation $dP/dt = P(x_2 - a_P)$, with a timescale of weeks.

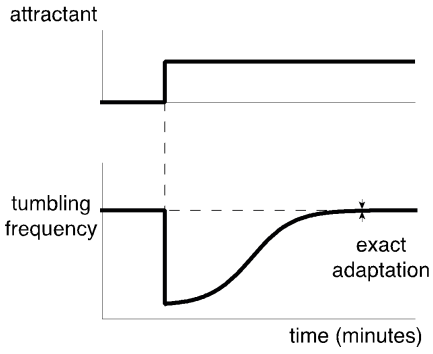

Figure 12.19

The exact-adaptation feature allows both the HPA axis and bacterial chemotaxis to convert a step change of input u into a pulse (Fig 12.19). This effectively computes a temporal derivative. Thanks to fold-change detection, the temporal derivative is actually of $log(u)$, allowing search over a very wide dynamic range.

The endorphins secreted by the HPA axis make sure that a person learns rewarding behaviors. This learning over weeks guides behavior up the increasing arm of the inverse-U shaped curve to optimal stimulus levels. This search process may be called **sitmulotaxis**.

What about too high levels of stimulation? If behaviors reach too high stimulation, such as unrewarding dangerous behaviors, other processes kick in, described in the previous lecture, including anxiety and depression. These processes are guided by the GR receptor that detects very high levels of cortisol. Depression and anxiety tend to shut down the exploration of potentially dangerous behaviors such as attacking the alpha male baboon.

Thus, the HPA axis provides a navigation system in behavior space. This navigation system can be hijacked by substances which provide pleasure and induce endorphins by activating the HPA axis over a timescale of weeks. The person learns to increasingly seek substance use, with the dire consequences of addiction.

Exercises:

12.1 **Initiation after withdrawal**: Discuss the duration of the initiation phase if relapse occurs during acute withdrawal versus after total recovery.

12.2 **Dual addiction**: suppose that two substances activate the HPA pathway. The doses taken are D_1 and D_2. The effect on the HPA axis is $u = (1 + D_1)(1 + D_2)$, where $u = 1$ is the baseline input before addiction.

(a) Discuss how the two substances affect each other's tolerance and withdrawal.

(b) What is the effect of stopping one substance while still using the other?

12.3 **Placenta**: During pregnancy, the placenta secretes x_1 (CRH) in an exponentially increasing concentration with time. What is the effect on x_2 and x_3? Is there exact adaptation? What is the evolutionary advantage of this exponential rise in terms of providing the mother and infant with increased cortisol and beta endorphins? What do you expect happens after birth when the placenta exits the body? Read about cortisol binding globulin (CBG) and pregnancy. How could this affect the answer?

12.4 **Fold change detection in the HPA axis:** Fold change detection (FCD) means that starting from steady-state initial conditions, the dynamic response of a certain variable to a given input u(t) is exactly the same as for the same input multiplied by a constant lambda u(t), with $\lambda > 0$. In this exercise we will show that the HPA model has FCD for the variables x1 and x2. Our strategy will be to use **scaled variables** to arrive at an equation that does not depend directly on input u, but on its **fold-change** relative to steady state $F = u/u_0$. The initial conditions and the equations depend only on fold change in input F, and thus the entire dynamics depend only on fold change.

The HPA model equations are:

$$\begin{aligned} \frac{dx_1}{dt} &= \frac{q_1 u}{x_3} - a_1 x_1 \\ \frac{dx_2}{dt} &= \frac{q_2 P x_1}{x_3} - a_2 x_2 \\ \frac{dx_3}{dt} &= q_3 A x_2 - a_3 x_3 \end{aligned} \quad , \qquad \begin{aligned} \frac{dP}{dt} &= P(b_P x_1 - a_P) \\ \frac{dA}{dt} &= A(b_A x_2 - a_A) \end{aligned}$$

(a) Find the steady-state solution for a constant input u_0. Show that x_1 and x_2 do not depend on u_0 whereas x_3, P and A are linear in u_0.

(b) Construct new equations by changing the variables, by normalizing A P and x_3 by u_0: define $\hat{x}_1 = x_1,\ \hat{x}_2 = x_2,\ \hat{x}_3 = x_3/u_0,\ \hat{A} = A/u_0, \hat{P} = P/u_0$.

(c) Plug in the new variables to the HPA model equations, to obtain scaled equations. Show that the scaled equations are identical to the original equations, except that instead of input u, they contain the fold-change, $F = u/u_0$.

(d) Show that the initial conditions (steady-state conditions) for the scaled equations do not depend on absolute input level u_0, only on fold change F.

(e) Conclude that if both the equations and the initial conditions depend only on F, so does the entire dynamics.

(f) Go back to the original variable and show that $x_1(t)$ and $x_2(t)$ depend only on fold change in input, whereas $x_3(t)$, A(t) and P(t) depend on the absolute input level.

(g) Explain intuitively how FCD works in this model. Consider that A, P and x_3 act as buffers that can normalize out the input absolute level.